EFFICIENT SYNTHESIS OF BLOCK-SEGMENTED DENDRIMERS

by

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To My Family

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ABSTRACT

EFFICIENT SYNTHESIS OF BLOCK-SEGMENTED DENDRIMERS

Highly branched, globular and monodisperse macromolecules are promising platforms for drug delivery. Due to these properties, evaluation of dendrimers as drug delivery agents is being actively pursued. This necessitates the development of efficient methods for dendrimer synthesis. This thesis proposes two novel methodologies that allow efficient synthesis of segment block dendrimers.

The first part of this study demonstrates that ‘click reactions’ such as Huisgen cycloaddition is an effective method for combining dendrons. Synthesis of ‘segment block’ dendrimers was realized in high yield and purity utilizing a [3 + 2] cycloaddition between azide and alkyne appended dendrons. Two different types of dendrons (poly (aryl ether) and polyether) were synthesized via convergent method up to third generation. These dendrons were equipped with the necessary functional groups and click reaction was utilized for the coupling of dendrons to obtain ‘nonsymmetrical segment block dendrimers’. Effect of generation and constitution of branching units of the dendrons on the cycloaddition was probed.

In the second part, attachment of different kinds of dendritic structures to a 1,3,5-trichlorotriazine based core to synthesize nonsymmetrical macromolecules was evaluated. 1,3,5-trichlorotriazine is known to have a chemoselective reactivity. As a result the degree of substitution on the molecule can be controlled by the applied temperature. We propose that segment block dendrimers can be prepared using as a 1,3,5-trichlorotriazine core molecule by taking advantage of this chemical reactivity difference.

ÖZET

VERİMLİ BLOK-DİLİMLİ DENDRİMER SENTEZİ

Çok dallı, küresel ve kesin olarak tanımlanmış moleküler ağırlığa sahip makromoleküller ilaç dağıtım sistemleri olarak kullanılabilme açısından gelecek vaat etmektedir. Sahip oldukları bu özelliklerden dolayı, dendrimerlerin ilaç taşıma sistemleri olarak kullanılması sıklıkla incelenen bir konu haline gelmiştir. Bu özellikleri, dendrimer sentezi için yüksek verimli sentez metotları geliştirilmesini gerektirir. Bu tezde ‘dilimli dendrimer’ sentezini sağlayan yüksek verimli iki yeni metot önerilmektedir.

Bu çalışmanın ilk bölümünde Huisgen siklo katılımı gibi bir ‘click reaction’ metodunun dendronları birleştirmek için efektif bir metot olduğu gösterilmiştir. Dilimli blok dendrimerlerin, azit ve alkin fonksiyonel gruplarına sahip dendronların [3 + 2] siklo katılımıyla yüksek verim ve saflıkta sentezlenebildiği anlaşılmıştır. İki farklı tip dendron (poli (aril eter) ve polieter) ’dıştan içe doğru’ metodu ile 3. jenerasyona kadar sentezlenmiştir. Bu dendronlar gerekli fonksiyonel gruplarla donatıldıktan sonra ‘simetrik olmayan dilimli dendrimer’ sentezleyebilmek için ‘click reaction’ metodu kullanılarak birleştirilmiştir. Dendronun jenerasyonunun ve dallanma birimlerinin yapısının siklo katılım reaksiyonu üzerindeki etkisi araştırılmıştır.

İkinci bölümde ise, 1,3,5-triklorotriazin molekülüne farklı dendritik yapılar eklemek suretiyle simetrik olmayan makromoleküller elde etmek için çalışmalar yapılmıştır. 1,3,5-triklorotriazin molekülü kimyasal olarak seçici reaktiviteye sahiptir. Bu sayede molekül üzerindeki yerine geçme derecesi uygulanan sıcaklık ile kontrol edilebilmektedir. 1,3,5-triklorotriazin’in kimyasal reaktivite farklılığı kullanılarak dilimli-blok dendrimerlerin sentezlenilebileceği ileri sürülmektedir.

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LIST OF SYMBOLS / ABBREVIATIONS

J	Coupling constant
σ	Chemical shift
υ	Frequency
DCC	N,N’-Dicyclohexylcarbodiimide
DMF	Dimethyl formamide
G	Generation
HOMO	Highest occupied molecular orbital
LUMO	Lowest occupied molecular orbital
MHz	Mega hertz
NMR	Nuclear magnetic resonance
OLED	Organic light emitting diode
PAMAM	Poly(amido amine)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethyl silane
UV	Ultraviolet

1. INTRODUCTION

Dendrimers, are regularly branched, highly ordered, globular 3-D macromolecules prepared by a stepwise synthetic procedure (Figure 1.1) [1]. Unlike linear, crosslinked or hyperbranched polymers, dendrimers are perfectly monodisperse and they have well-defined structures. Synthesis of the first dendrimer in the literature was done in 1980s and since then tremendous amount of work has been published [2]. Dendrimers have a compact, 3-D globular structure and thus they provide a rich source of surface functionality making them useful for many applications such as targeted drug delivery, modification of the surfaces, model light harvesting systems, etc.

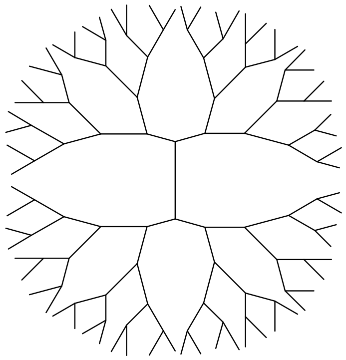

Figure 1.1. Structure of a dendrimer

1.1. Structure of Dendrimers

A dendrimer consist of three major architectural components which are: a core, layers of branching repeat units and surface groups on the outer layer (Figure 1.2). The ‘core’ determines the multiplicity of the dendrimer via the number of functional groups on it. For the growth of the dendrimer to the higher generations ‘branching units’ are needed. These branching units construct the 3-D shape of the dendrimer, which looks like a tree, and thus giving the ‘dendritic’ shape to the structure. The third component is the ‘surface groups’ which are primarily responsible for the dendrimer’s chemical reactivity. Since the core and the branching repeat units are sterically hindered they are generally chemically inactive, the functional groups at the surface of the dendrimers interact with surroundings and governs the physical properties and chemical reactivities. For the dendron, which can be represented as one whole branch of the dendrimer, the things are a little bit different. Instead of a 'core' the dendron has a 'focal point' which in most cases is chemically active enough to couple with a core and form a dendrimer.

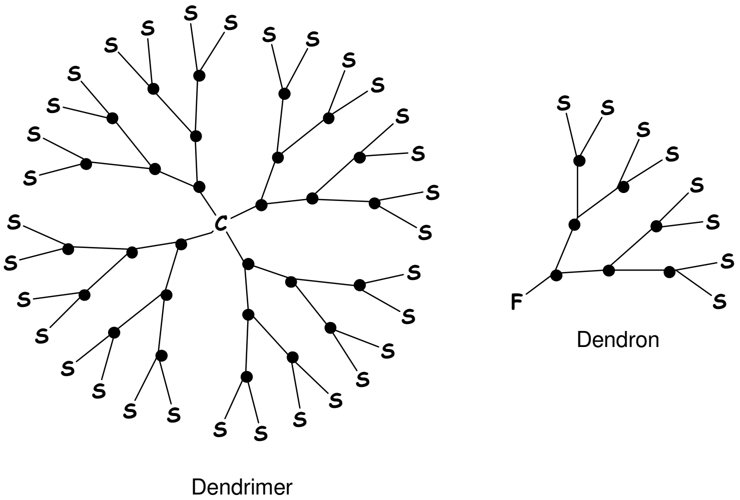

Figure 1.2. Schematic representation of dendrimers and dendrons

Each branching point at a dendrimer is named as a new generation. A dendrimer with no branching points is called 'generation zero'. As the number of branching points increases the generation of the dendrimer also increases (Figure 1.3). For example for a dendrimer which has three branching points the generation number is also three.

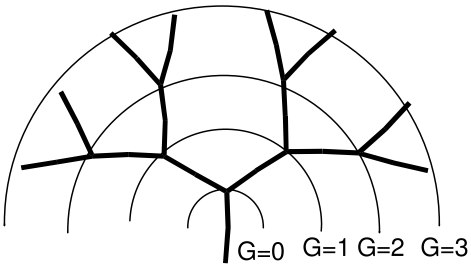

Figure 1.3. Generations of a dendrimer

1.2. Historical Development

The first generally accepted dendrimer synthesis was done by Vögtle in 1978 [3]. He named the products as 'cascade molecules' and used an iterative synthesis to synthesize them. However these molecules didn't attract attention particularly because of having branched structures. Then, in the following years three patents were filed on the synthesis of lysine dendrimers using the α and ε amino groups as the branching units for the structure [4]. In 1985, the word 'dendrimer' was given to these branched structures by Tomalia and coworkers [2]. They synthesized the poly (amidoamine) dendrimer which was abbreviated as PAMAM (Figure 1.4). In the same year Newkome and coworkers [7] published the synthesis of molecules termed 'arborols' which possess three branching points at each generation. After these two publications dendrimers gained a huge attention and tremendous amount of work was done related to dendrimers.

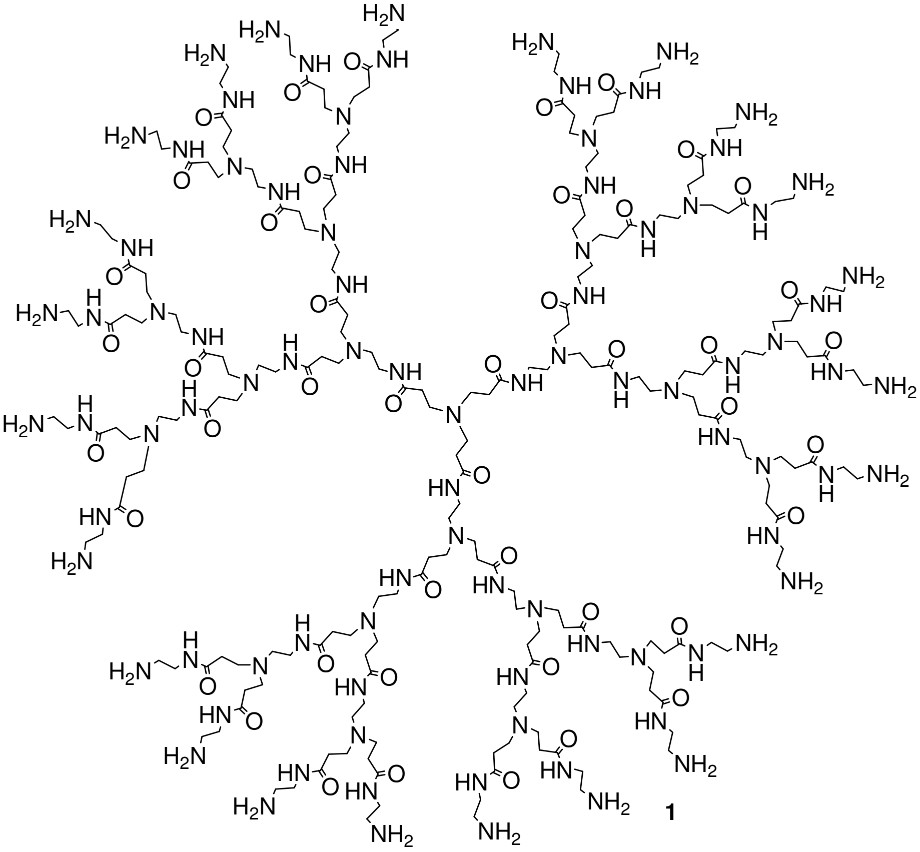

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Figure 1.4. Tomalia's third generation PAMAM dendrimer

1.3. Synthesis Strategies

Dendrimers can be synthesized by using two different approaches: the 'divergent' and the 'convergent' method. The first examples of dendrimers were synthesized via the divergent approach. In the divergent method the construction of the dendrimer starts from the core and branches out to the surface of the dendrimer. The other strategy which was developed in the following years is called the 'convergent method'. In the convergent method the synthesis starts from what will become the periphery of the dendrimer and the coupling of these small dendrons into a multivalent core produces the dendrimer. These two main strategies will be discussed in detail below.

1.3.1. Divergent Method

In divergent method the construction of the dendrimer starts from its core (Figure 1.5). Reaction of the functional groups at the periphery of the core with the active group of the monomer results in the formation of new branch points. The monomers generally have one active and two inactive groups. The peripheral functionalities on each monomer are made inactive to avoid uncontrolled hyperbranching. After the formation of new branching points these inactive groups are activated and by the reaction with the same monomer new peripheral groups are obtained. In this way, by alternating activation and coupling steps higher generations of dendrimers are obtained. For example, PAMAM dendrimer **1** (Figure 1.4) was synthesized via the divergent method.

Since the molecular weight of the dendrimer doubles with the production of each generation, divergent method is very suitable for large scale production of dendrimers. However, a large excess of reagents are required to drive both the activation and the coupling reactions into completion. The monomers used for the synthesis are smaller in molecular weight compared to the formed dendrimer and thus they can be purified from the mixture by simple methods such as distillation, precipitation or ultrafiltration.

While constructing a dendrimer with the divergent method, the number of the coupling reactions increases exponentially with each generation and thus the possibility of having incomplete functionalizations and side reactions also increase. As a result structural defects may occur on the dendrimer which causes polydispersity.

Divergent method, while bringing the advantages of mass production and easy purification techniques, also brings the disadvantage of creating polydisperse structures. The consumption of a large excess of the monomers is also another drawback of this method.

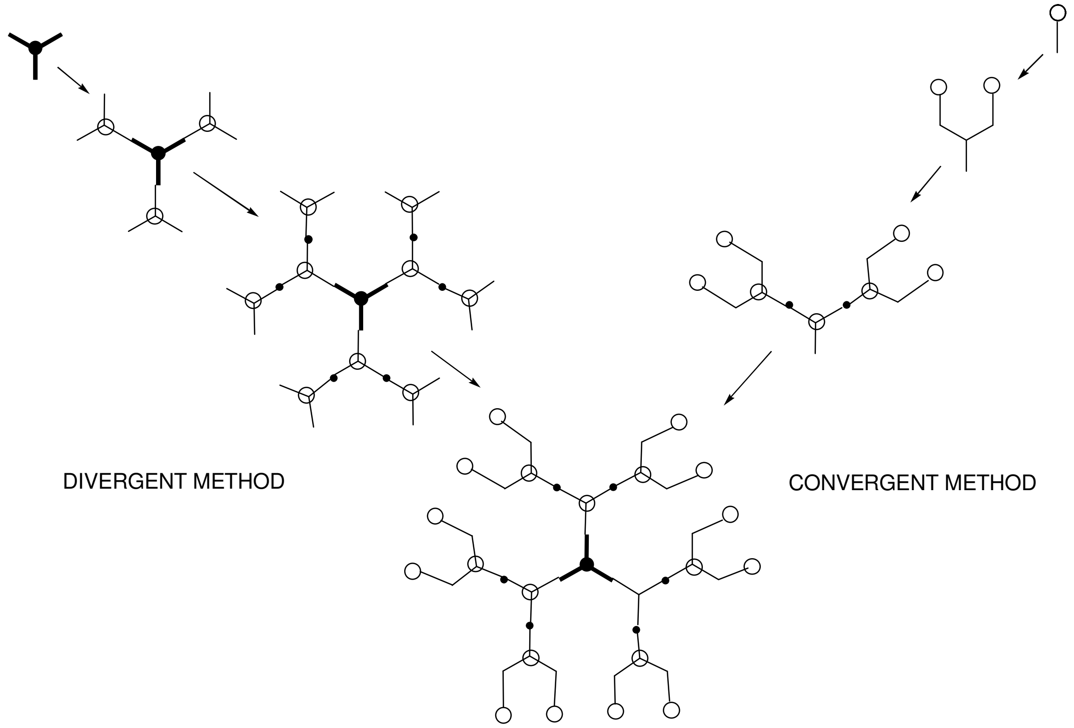
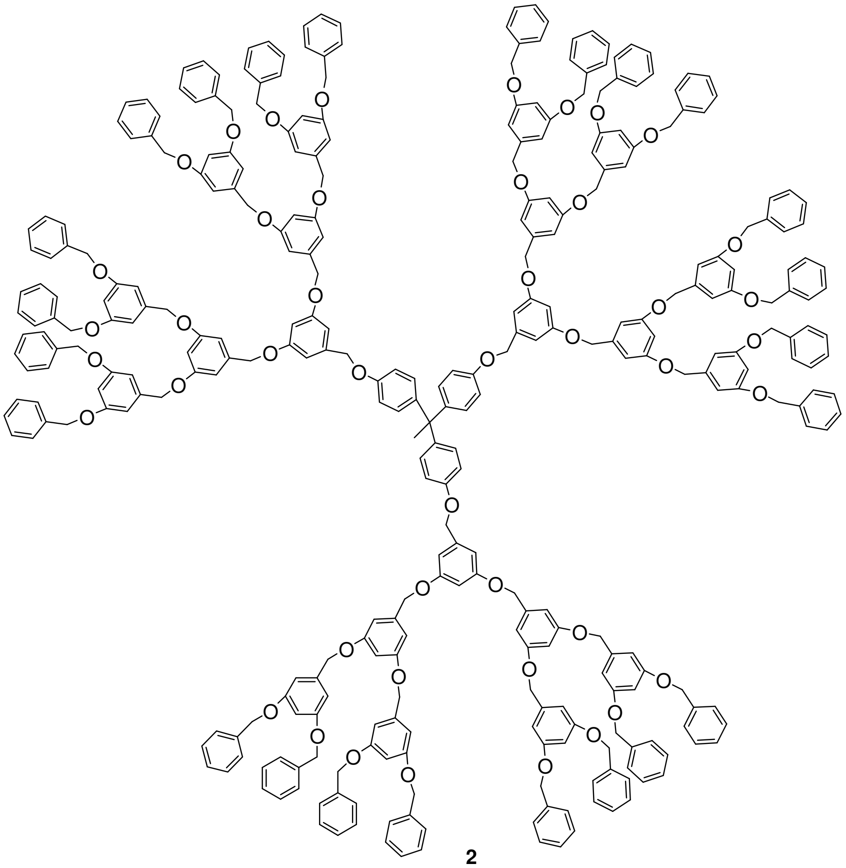


Figure 1.5. Divergent vs convergent method

1.3.2. Convergent Method

The convergent method was developed by Fréchet and Hawker in 1990 [8]. They synthesized a poly (aryl ether) dendron **2** (Figure 1.6), which was later on called the Fréchet type of dendron, via the convergent method. The main difference of the convergent method with respect to the divergent method is that in convergent method the synthesis of the dendron starts from what will become the periphery of the molecule and proceeds towards the inside (Figure 1.5).

The monomer as in the divergent method has two inactive and one active group. First the multiple surface groups are coupled onto the branching points of the monomer. After the coupling is completed the inactive group of the monomer is activated and another coupling step with the surface groups takes place. To obtain the higher generations these coupling and activations steps are followed alternately. Finally the convergently synthesized dendrons are coupled onto a multifunctional core to yield the desired dendrimer.



2

Figure 1.6. Fréchet's poly (aryl ether) dendrons attached onto a multifunctional core

The main drawback of the convergent method is the use of difficult purification techniques for isolating the dendrons. The reason is the low molecular weight difference between the starting dendrons and the final product. In divergent method this difference is very large that's why excess of the monomers can be purified by simple techniques, however in convergent method this difference is comparably small and so column chromotography is used to isolate the dendrons.

The main advantage of the convergent method is that at the end of these difficult purification techniques one can obtain a perfectly functionalized, monodisperse dendron. Also the reactions can be driven to completion with only a slight excess of the reagent which is another important feature of the convergent method.

2. BLOCK DENDRIMERS

Dendrimers can be used for a variety of applications not only because they have a perfect, monodisperse structure, but also they have a lot of functional groups at their periphery. Thus having an increased number of surface functionality on a dendrimer surface is a desirable thing. Dendrimers that are made up of different building blocks can be called as dendritic copolymers or in other words block dendrimers. There are three major groups of block dendrimers: layer block, segment block and surface block.

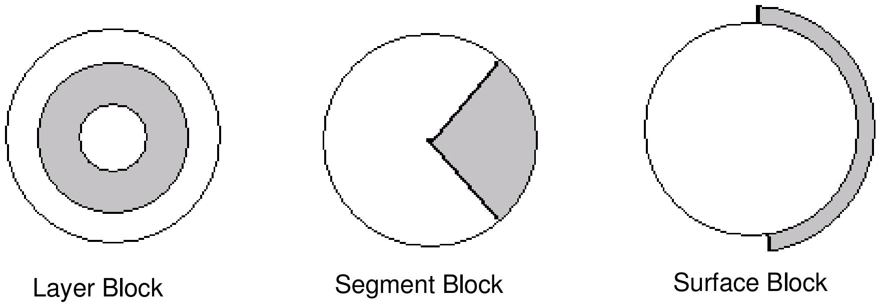


Figure 2.1. Types of block dendrimers

2.1. Layer Block Dendrimers

In layer block dendrimers, the dendrimer consists of more than one type of repeating units which are layered throughout the structure from the core to the periphery. They can also be synthesized by reacting the surface groups of a dendron with the core of another dendron and then attaching these larger dendrons onto the same core. Although there are examples of layer block dendrimers which are synthesized by the divergent method, they are generally synthesized by the convergent method. The synthesis of the first layer block dendrimer was done by Hawker and Fréchet in 1992 (Figure 2.2) [9]. In this study the preformed poly (benzyl ether) dendrons were convergently attached onto a poly (benzyl ester) monomer and then the synthesis followed by the coupling of this dendron onto a triphenolic core.

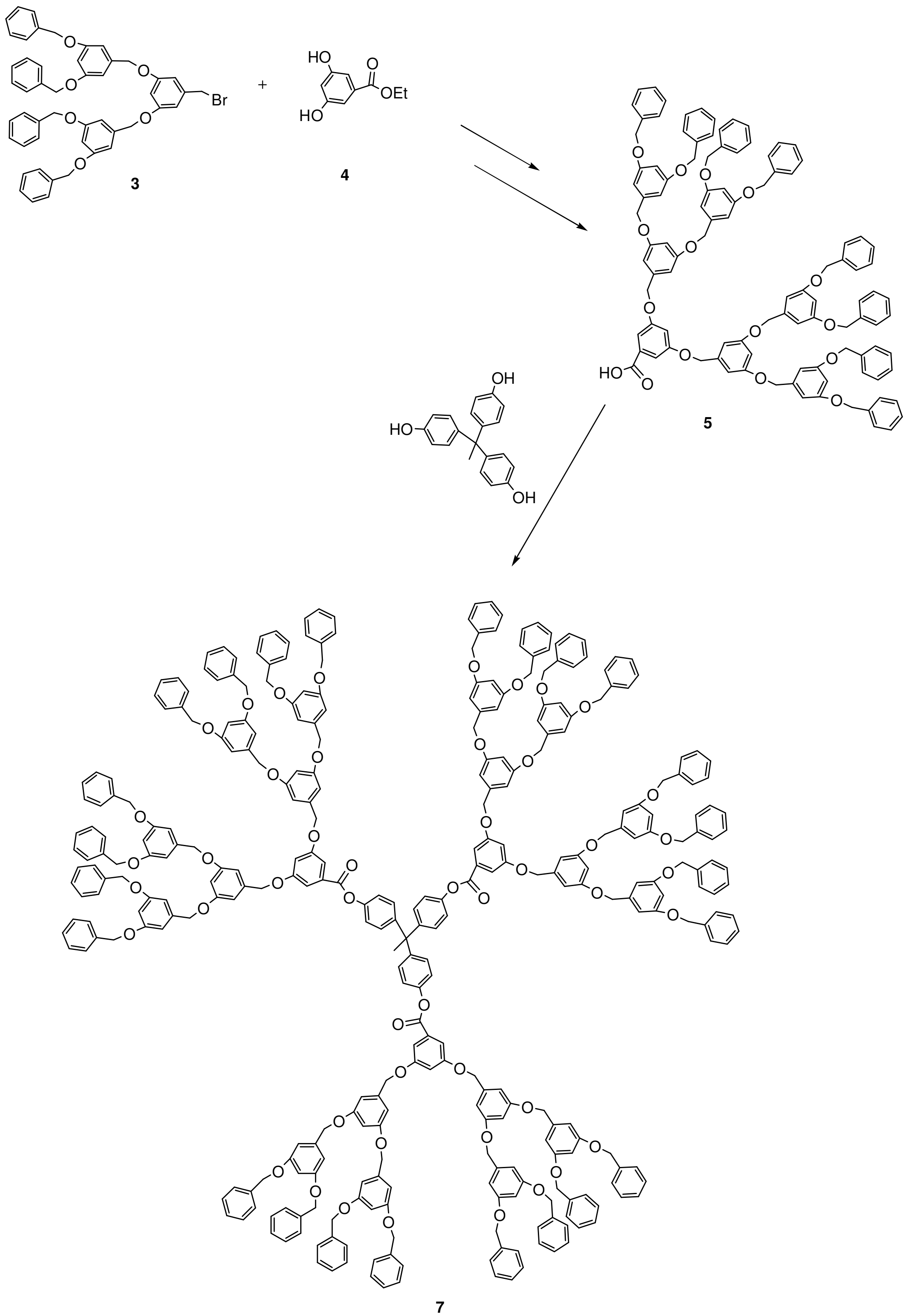


Figure 2.2. Synthesis of the first layer block dendrimer

A recent example of layer block dendrimers is obtained by Yamamato and coworkers [10]. First, they synthesized several generations of dendrimers with phenylazomethine architecture and then, they coupled these dendrons convergently by dehydration reaction with $TiCl_4$ on to a tetrakis(4-aminophenyl)methane core to obtain dendrimers which has rigid structure (Figure 2.3). These types of dendrimers are important for 'internal cavity' usage. The dendrimers with flexible architecture give rise to 'back-folding' and thus no internal cavity is observed whereas in this phenylazomethine dendrimer because of the rigid structure it has, there is no chance of losing the internal cavity.

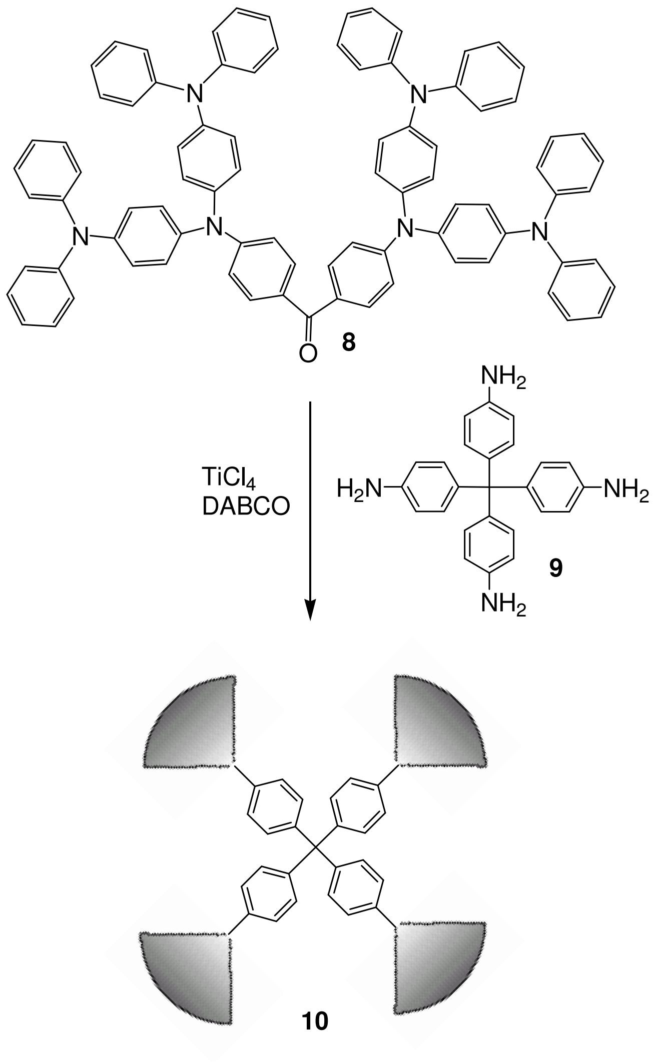


Figure 2.3. Synthesis of the phenylazomethine dendrimer

2.2. Segment Block Dendrimers

Segment block dendrimers are composed of different types of dendrons which are associated onto the same core. These types of dendrimers are unsymmetrical, and usually have more than one type of functional group at their periphery. They are generally synthesized by the convergent route so that after the first dendron is attached on to the multifunctional core, another dendron with a chemically different backbone can also be coupled to the core. This would have been very difficult to do with divergent method because of the side reactions that may have occured.

The first segment block dendrimer was synthesized by Hawker and Fréchet (Figure 2.4) [9]. In this study, the second generation Fréchet type poly (aryl ether) bromide was reacted with poly (benzyl ester) which was used in excess as a monomer. The singly coupled product is obtained which was then again coupled with a second generation poly (benzyl ester) carboxylic acid by a DCC mediated esterification yielding the unsymmetrical hybrid dendron. After activating the focal point of this dendron it can be further coupled onto a trisphenolic core to yield a dendrimer with three pairs of hybrid ester-ether dendritic blocks.

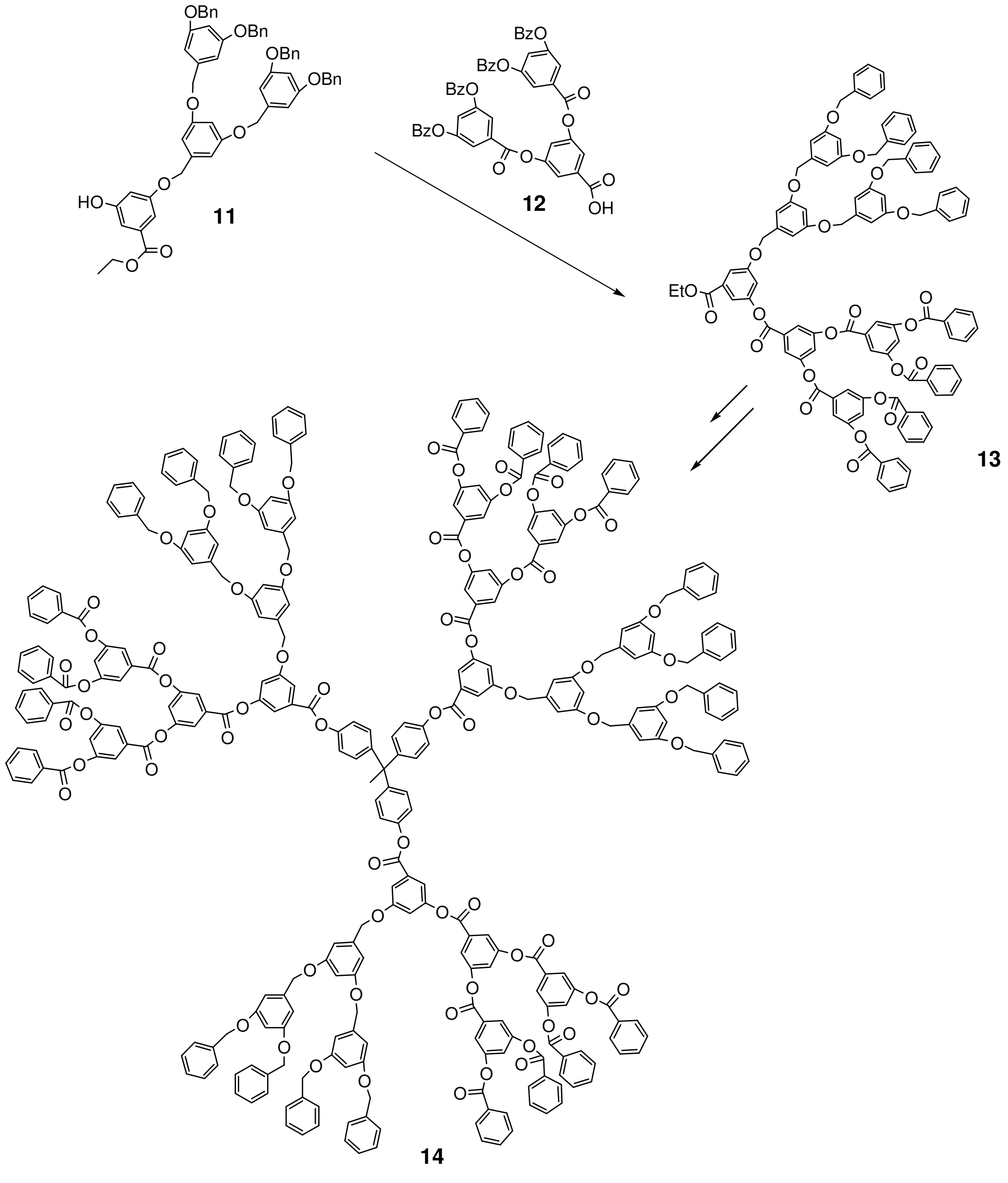


Figure 2.4. Synthesis of the first segment block dendrimer

In another study, Yamamoto and coworkers [11] synthesized an asymmetrically arranged dendrimer by coupling a carbazole and a phenylazomethine dendron via using $TiCl_4$ mediated dehydration reaction (Figure 2.5). It has been found that the complexation of the dendrimer changes the HOMO/LUMO energy gap of the dendrimer. So this segment block dendrimer can be used for organic light-emitting diode (OLED) applications.

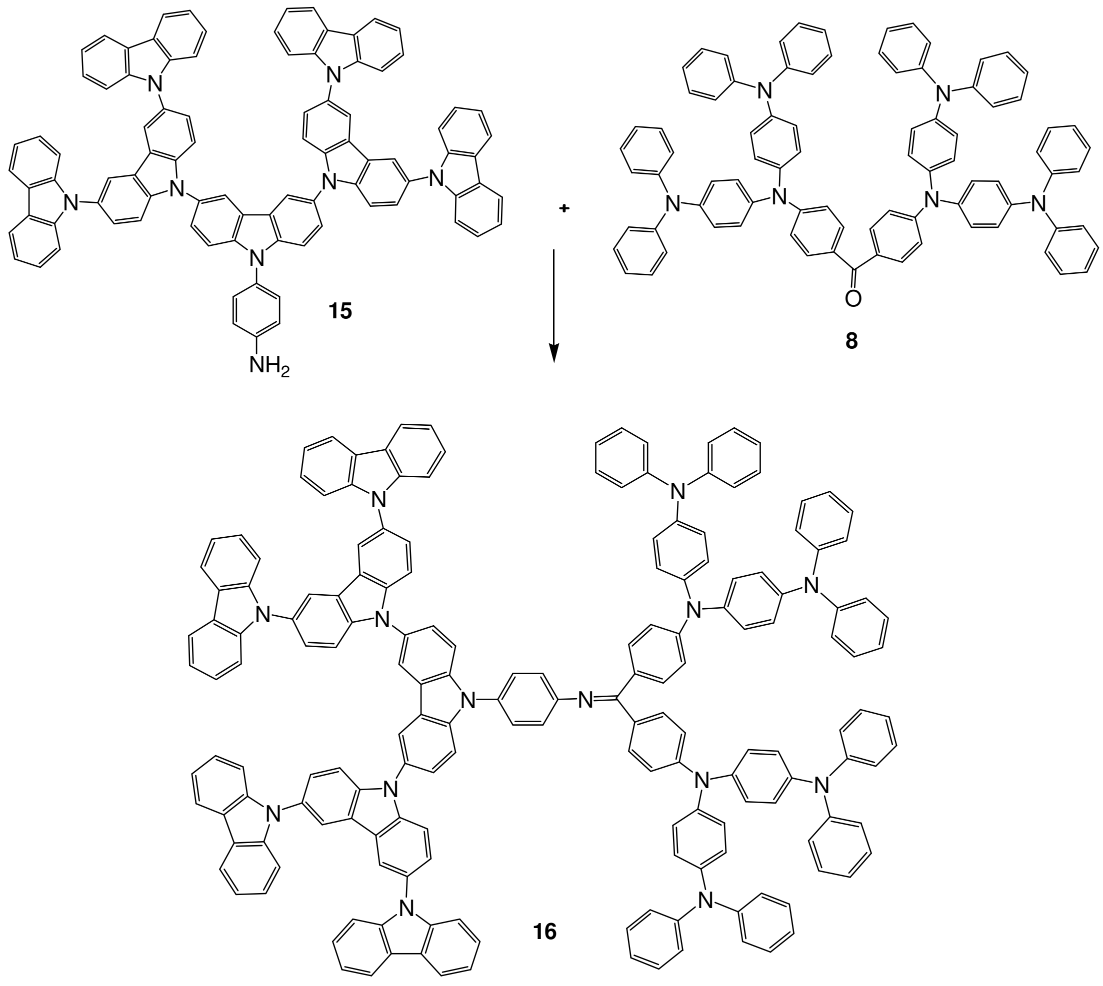


Figure 2.5. A segment block dendrimer by Yamamoto

2.3. Surface Block Dendrimers

In a surface block dendrimer two different types of end groups are located in definite areas on the surface of the dendrimers. These can be obtained by grafting dendrons with different end groups together. These type of dendrimers are similar to segment block dendrimers. The only difference is in segment block dendrimers different dendrons were attached on to the same core whereas in surface block dendrimers the surface modified versions of the same dendron can be coupled to the starting dendron to obtain unsymmetrical dendrimers. Surface block dendrimers have homogeneity in the inner structure of the dendrimer.

Wooley et al. [12] synthesized a surface block dendrimer which contained p-cyanophenyl electron withdrawing groups on one hemisphere and the other was is 3,5-bis(benzyloxy)phenyl electron-donating groups (Figure 2.6). The resulting dendrimer had a strong dipole due to its globular shape and structural segregation of different end groups.

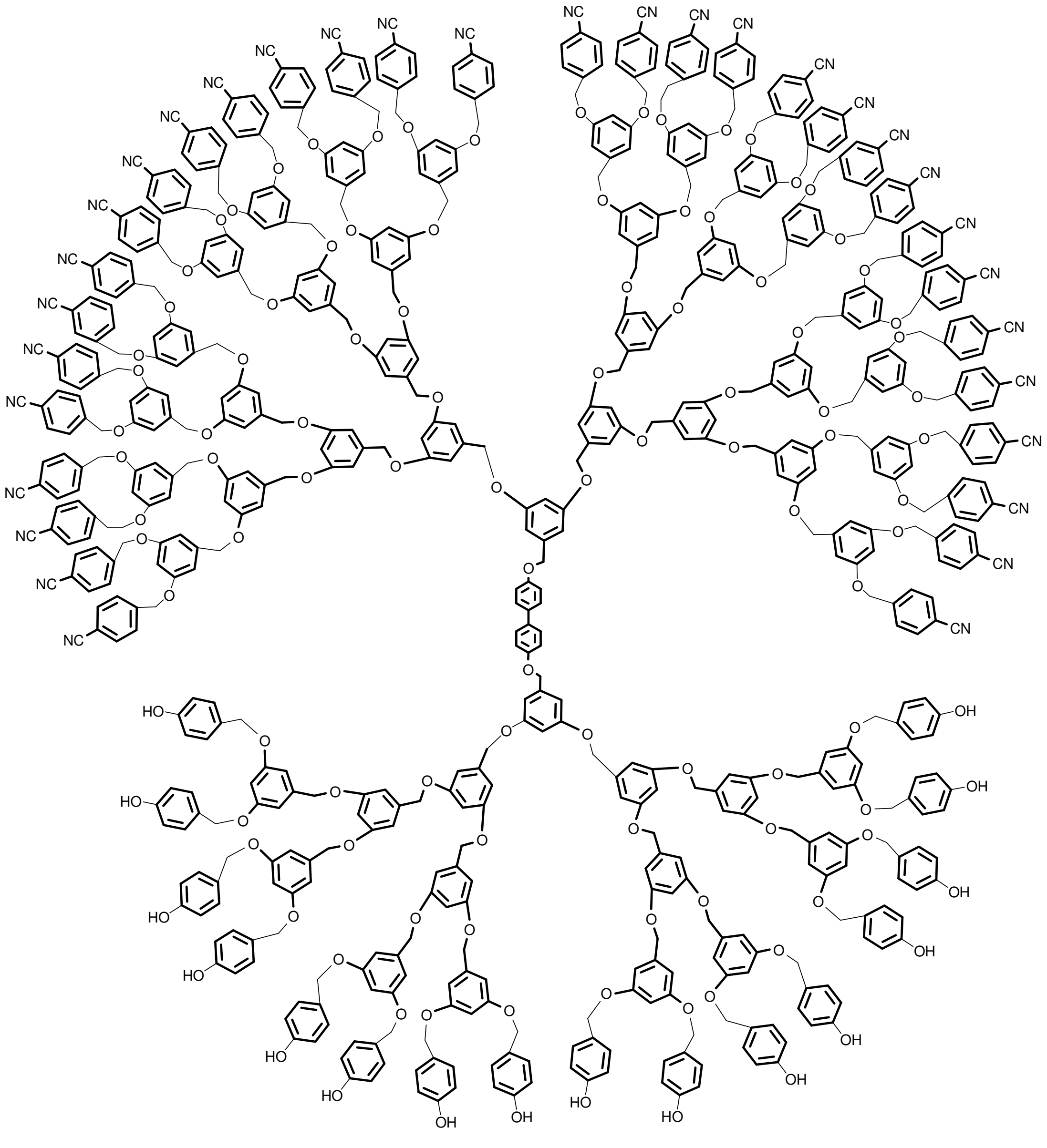


Figure 2.6. A strongly dipolar surface block dendrimer

3. CLICK CHEMISTRY

Huisgen 1,3-dipolar cycloadditions provide easy access to a variety of five-membered heterocycles by coupling two unsaturated reactants [13]. The cycloaddition reaction between azides and terminal alkynes to give disubstituted triazoles is the most ideal click reaction known to date. However this reaction generates a mixture of 1,4 and 1,5-disubstituted triazoles.

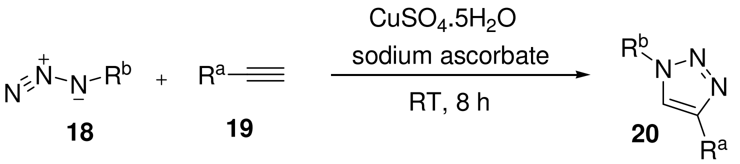


Figure 3.1. Click reaction between an azide and a terminal alkyne

In 2002 Sharpless and coworkers [14] found that Cu (I) catalyzed reaction systems regiospecifically combines azides and terminal alkynes to give only 1,4-disubstituted 1,2,3-triazoles (Figure 3.1). While a number of Cu (I) salts such as CuI, CuOTf.C_6H_6, $[Cu(NCCH_3)_4][PF_6]$ can be used directly for this reaction later on it is realized that the catalyst is better prepared in situ by the reduction of Cu (II) salts, such as $CuSO_4.5H_2O$, which are less costly and often purer than Cu (I) salts. Ascorbic acid or sodium ascorbate was used as a reductant. A broad spectrum of 1,4-triazole products and high yields were achieved with less than 2mol % catalyst loading. The reaction is insensitive to air and H_2O which makes it even simpler and easy to handle. Also there is virtually no byproduct and the purification process is easier. So all these properties make the click reaction very attracting and many examples are being produced each day.

The mechanism of the copper catalyzed reaction starts with the formation of copper (I) acetylide (Figure 3.2). Then the stepwise combination of the azide takes places through the route 1 → 2 → 3 → 4 instead of the concerted [2 + 3] cycloaddition which goes directly from 1 to 4. Density functional theory calculations also show that the reaction follows the route 1 → 2 → 3 → 4 which proceeds through the six-membered copper containing intermediate.

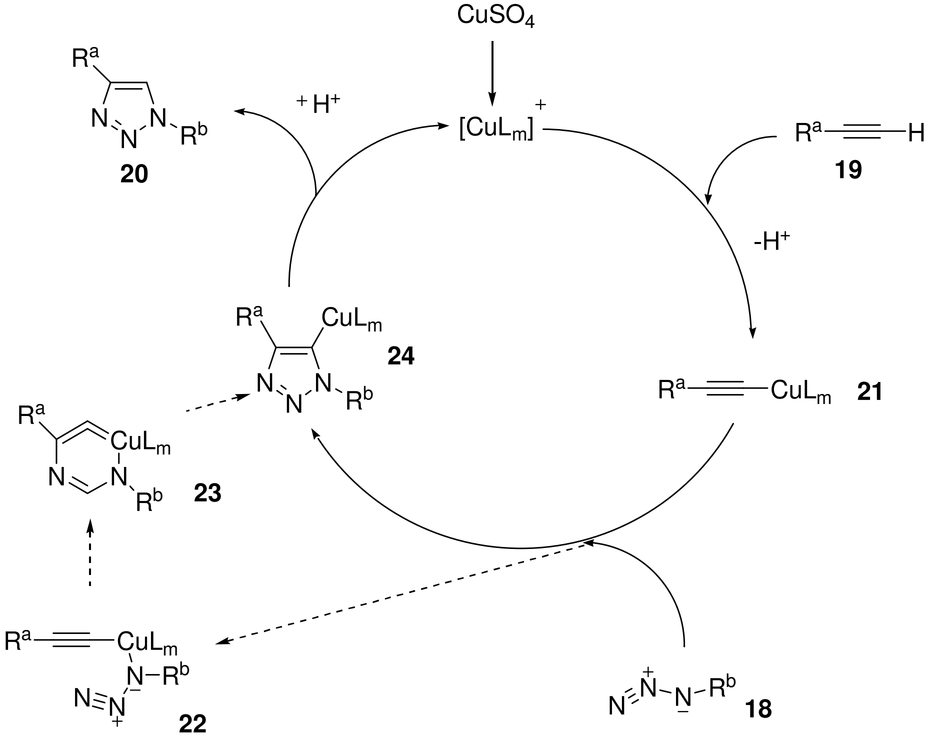


Figure 3.2. Postulated catalytic cycle for azide-alkyne coupling

Since click chemistry allows the rapid synthesis of compound libraries it has found many applications in organic chemistry, drug discovery, bioconjugations, material science and synthesis of polymers and dendrimers.

As explained in chapter 1, unique properties of dendrimers which are mainly due to their structural features increased the interest on dendrimer chemistry. A large number of dendritic structures have been synthesized. However most dendrimer synthesis in later generations require high monomer loading, rely on difficult separation strategies and generate a considerable amount of side products. It has been experienced that the use of click chemistry for dendrimer synthesis is an excellent method for obtaining high yields, purity and nearly quantitative yields.

In 2004, Sharpless and coworkers [15] used click chemistry for the convergent synthesis of a large library of triazole dendrimers (Figure 3.3). The individual dendrons were built sequentially, starting on the outside of the molecule. Then, they were coupled into a multivalent core via click chemistry to yield dendrimers with different end groups and internal repeat units. For the synthesis of the dendrons different types of AB_2 monomers were used which have terminal alkynes and alkyl halide functionalities. The presence of the single chloromethyl group in the monomers allowed the activation of the focal point so that the convergent growth approach was established perfectly. The reaction of the chloromethyl group with NaN_3 gave the azidomethyl group which was coupled with the acetylene functionalized dendrons via click chemistry to yield the next generation. $CuSO_4.5H_2O$ (2-5 mol %) and sodium ascorbate (5-10 mol %) were used in 1:1 mixture of water and t-butyl alcohol at room temperature to generate the desired disubstituted triazoles in nearly quantitative yield. They also generated examples using azide functionalized compounds as monomers and grew dendrimers via click reactions.

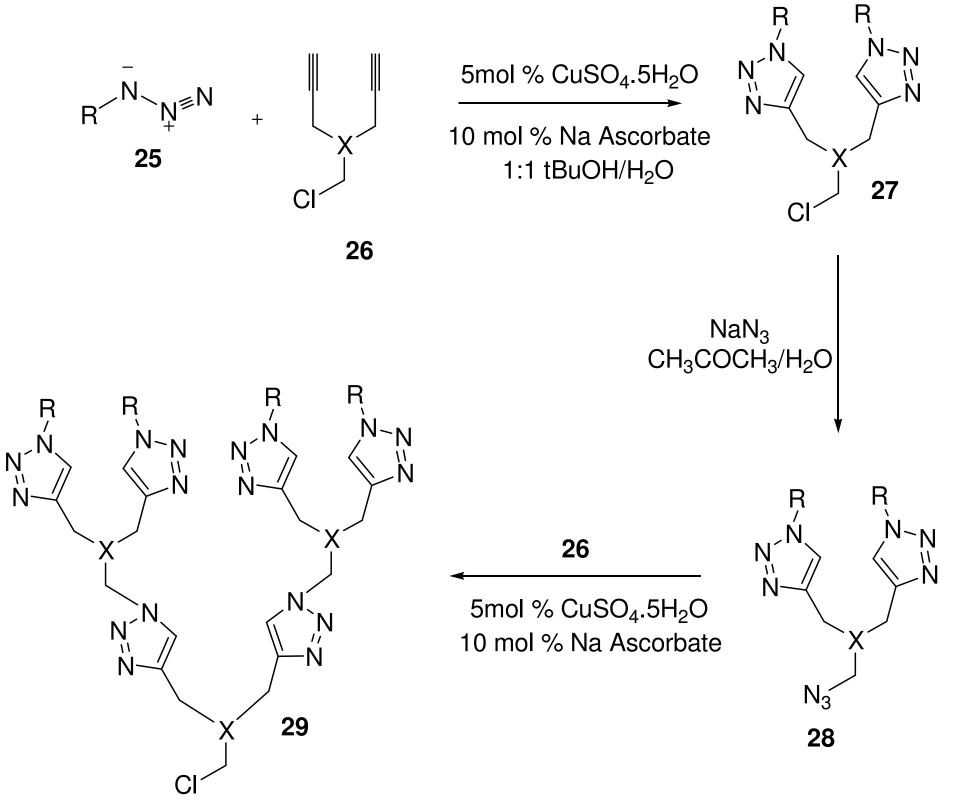


Figure 3.3. Synthesis of triazole dendrimers via click chemistry

In another study, Hawker and Fréchet [16] synthesized dendronized linear polymers via click chemistry (Figure 3.4). Dendronized linear polymers have recently emerged as new materials for nanoscale applications such as catalysis, drug delivery and nanoscale electronics. A 'graft-to' approach was used where a dendron is attached to a polymer via the pendant groups on the polymer. To apply the click chemistry concept they synthesized a Fréchet type dendritic azide which was then reacted with the pendant alkynes of poly-(vinylacetylene). The reaction gave quantitative yields for generation 1 and 2 azides and for generation 3 the yield was greater than 98 % as usually observed for click chemistry reactions.

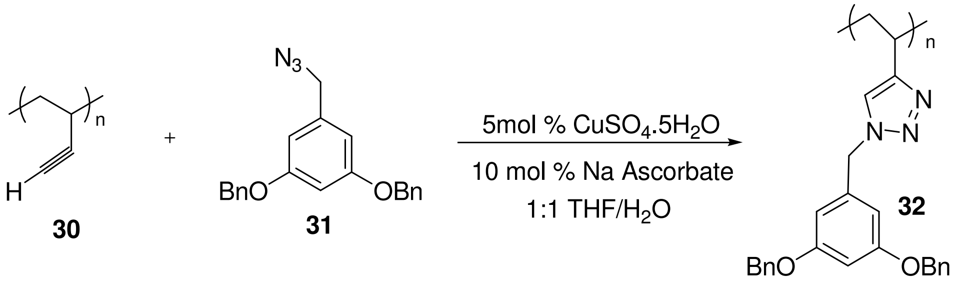


Figure 3.4. Dendronized linear polymers via click chemistry

In 2005, PEG and peptide grafted aliphatic polyesters were synthesized using click chemistry (Figure 3.5) [17]. The properties of PEG polymers such as biocompatibility, biodegradability and resistance to protein adsorption make them very useful for biomaterial and drug delivery applications. Hence in this work, acetylene functionalized lactones were polymerized and then, azide terminated PEG chains were grafted on to this polymer chain. The same strategy was also applied for synthesizing peptide grafted polymers in which a certain azide functionalized peptide was grafted on to the acetylene functionalized PEG via click chemistry. As a result PEG polymers which have different pendant groups on them were synthesized.

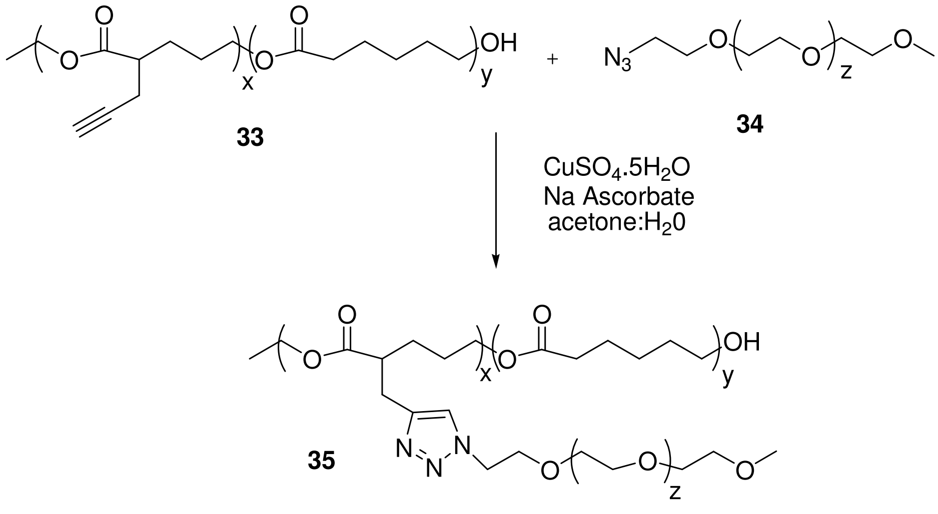


Figure 3.5. PEG and peptide grafted aliphatic polyesters via click chemistry

During the course of our study Hawker and coworkers [18] reported the synthesis of multivalent, bifunctional surface block dendrimers (Figure 3.6). Unsymmetrical dendrimers which has different types of functionality on their surface is important for targeted drug delivery purposes. Three functional units on the dendrimers are required: a targeting moiety, a medicinally active agent (drug) and a diagnostic label. Each of these should be attached at a specific position within the structure. In order to achieve this, a dendritic block copolymer which has two different clusters of functionality at the chain ends is synthesized. The anhydride of 2,2-bis(hydroxymethyl)propionic acid is used which gives easy access to both the alkyne and the azide by condensation with the appropriate alcohol [19]. Then, after the removal of the acetonide protecting groups and acylation with the anhydride, growth of the dendrons which have either a single azide or acetylene at their focal point is achieved. The dendrons were synthesized up to 4th generation and different coupling reactions were tried. In this way dendrimers which has the dual functionality of recognition and detection were synthesized as candidates for drug delivery purposes.

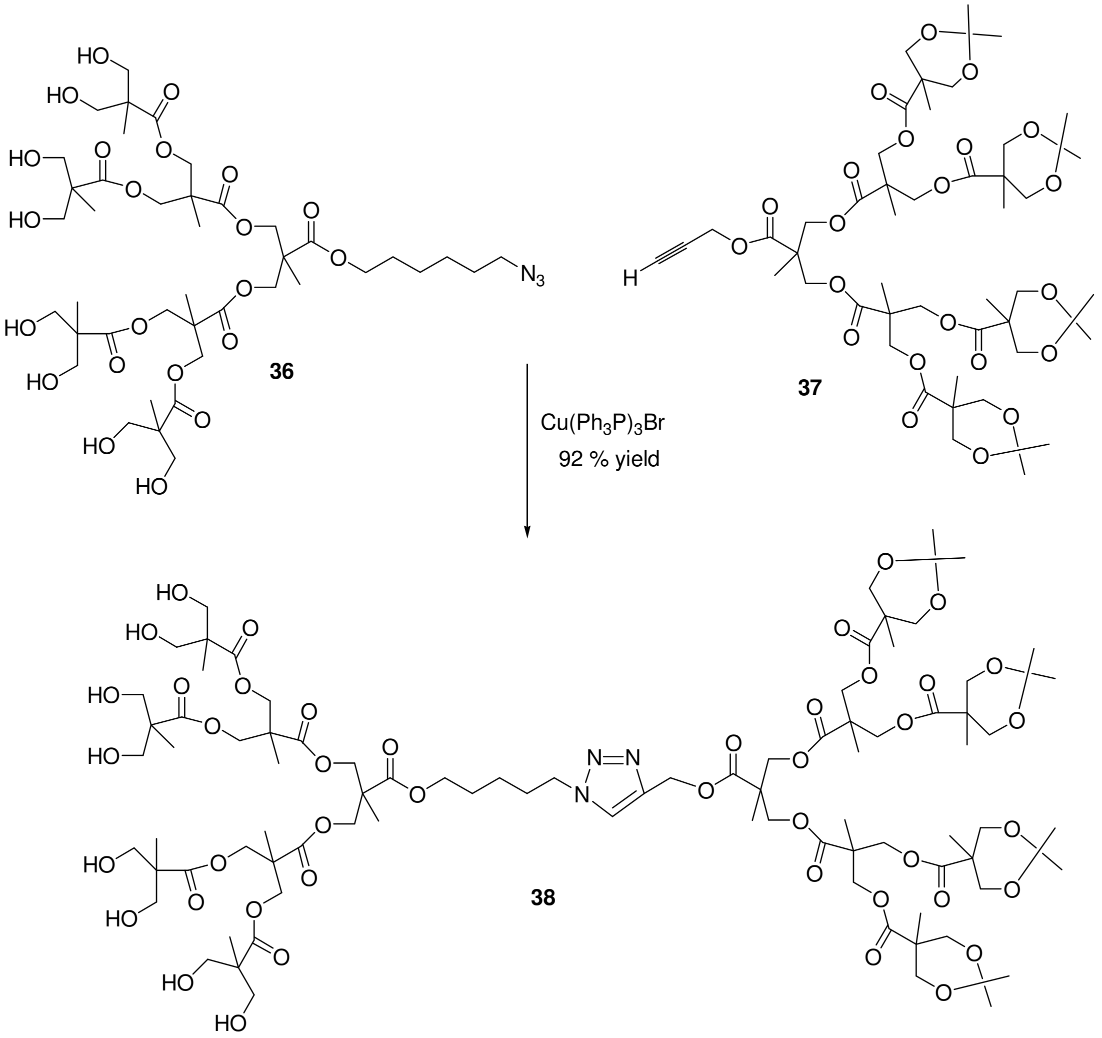


Figure 3.6. Multivalent, bifunctional surface block dendrimers

As can be seen from the examples, click chemistry is a very useful reaction to synthesize multifunctional molecules in high yields, purity and less effort. During the course of our study, it has been shown to be an excellent method for the synthesis of multivalent bifunctional surface block dendrimers by Hawker and coworkers. In our study we will be synthesizing an unsymmetrical diblock dendrimer as opposed to surface block dendrimer by combining two different dendrons via click chemistry. The application of this methodology is discussed in the next chapter.

4. RESULTS AND DISCUSSION – PART A

4.1. Aim of the Study

The aim of this study is to synthesize nonsymmetrical segmented block dendrimers using ‘click chemistry’. Two different types of dendrons (poly (aryl ether) and polyether) were synthesized via convergent method up to third generation. These dendrons were equipped with the necessary functional groups and click reaction was utilized for the coupling of dendrons to obtain ‘nonsymmetrical segment block dendrimers’ (Figure 4.1). Effect of generation and constitution of branching units of the dendrons on the cycloaddition was investigated. The experimental details are given in the following sections.

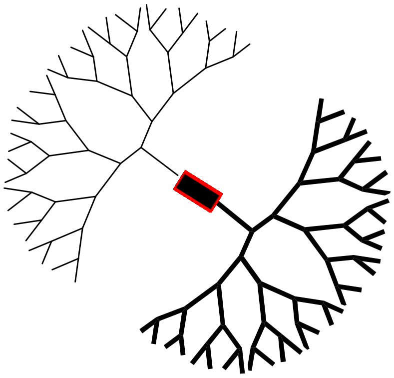


Figure 4.1. A nonsymmetrical segment block dendrimer

4.2. General Methods and Materials

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-Mx operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, using deuterated chloroform as solvent in the Advanced Technologies Research and Development Center at Boğaziçi University. Infrared spectra were recorded on KBr plate on a Perkin-Elmer 1600 FT-IR Spectrophotometer. Flash chromatography was performed using silicagel-60 (43-60 nm).

Thin layer chromatography was performed using silica gel plates (Kiesel gel 60 F_{254}, 0.2 mm thick, Merck). Plates were viewed under an ultra violet lamp at 254 nm.

Chemicals were used as received (Merck, Aldrich, Lancaster, Alfa Aesar, Avocado, Riedel de Haen). CH_2Cl_2 (Merck) was distilled over CaH_2 prior to use. Acetone (Merck) was distilled over dry K_2CO_3 prior to use. THF (Riedel de Haen) was distilled over sodium/benzophenone prior to use. DMF (Riedel de Haen) were distilled over molecular sieves (4 A^0). Solvents used for purification, hexane, ethyl acetate, CH_3OH and CH_2Cl_2 were distilled prior to use (Akkimya).

4.3. Synthesis of Dendrons

4.3.1. Poly (aryl ether) Dendron

Fréchet type of poly (aryl ether) dendron was synthesized for the first time in 1990 by Fréchet and Hawker. They not only synthesized a new dendron but also introduced a new methodology for the synthesis of dendrons and dendrimers which was the 'convergent method'. The poly (aryl ether) dendrons are of choice because they exhibit the chemical stability associated with the ether linkages and they have good solubility in many organic solvents. The poly (aryl ether) dendrons reported here were synthesized by the adaptation of the procedures used by Fréchet and Hawker [8].

In our study, 3,5-dihydroxybenzoic acid **39** is converted in to the corresponding ethyl ester **40** via reacting with ethanol (Figure 4.2). Alkylation of the phenolic groups of this ester with benzyl bromide yielded in the first generation ester **42** of our dendron. In the following step, this so called G_1-ester is converted in to the G_1-alcohol **43** via $LiAlH_4$ reduction. Then, the benzylic alcohol functionality, at the focal point of our dendron, is activated via its conversion to the corresponding bromide leaving group. After the coupling reaction of our monomer, which is 3,5-dihydroxybenzyl alcohol **45**, with two equivalents of this activated G_1-bromide **44** the synthesis of the second generation alcohol **46** is achieved (Figure 4.2). Following the same activation and coupling steps second generation bromide **47** and third generation alcohol **48** are also synthesized (Figure 4.3).

As can be seen from the procedure we are constructing our dendron by the alternating reactions which are the activation of the focal point of the dendron by bromination and then, the coupling of our monomer with this activated dendron. The construction of the dendron starts from what will become the periphery of the dendron which brings us the advantages of convergent method that are discussed in the first chapter. Synthesis steps will be explained in subsequent sections.

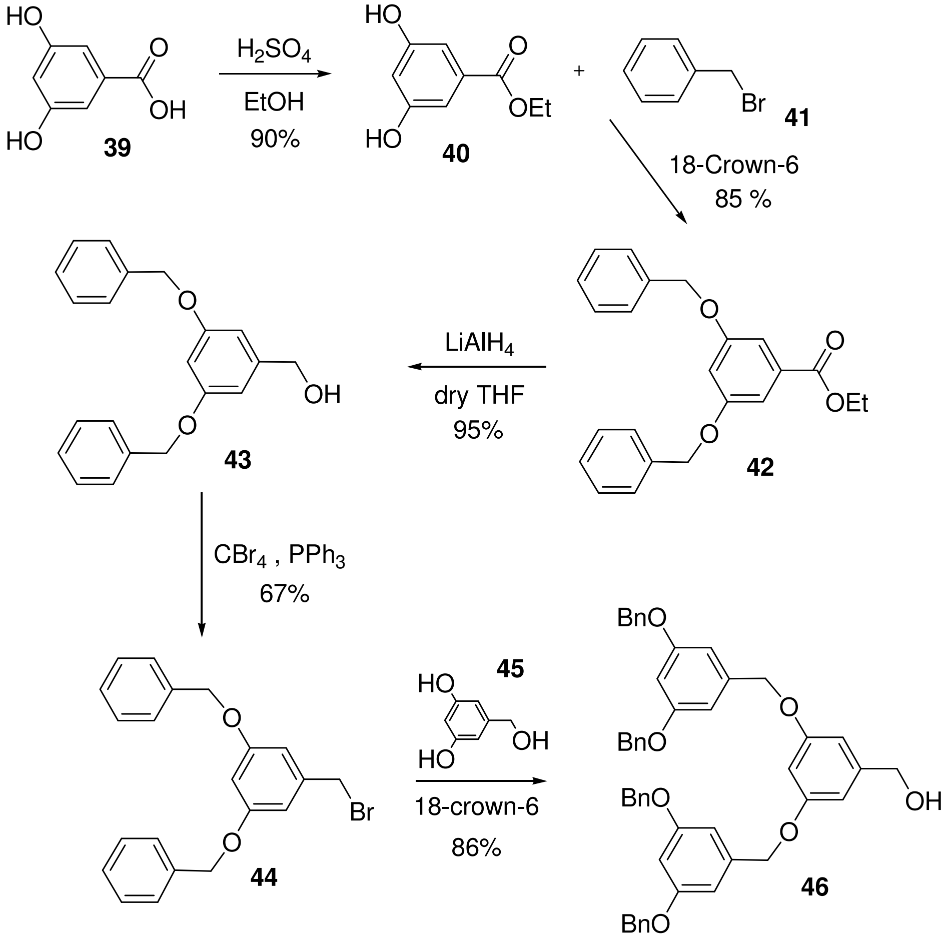


Figure 4.2. Poly (aryl ether) dendron synthesis: Lower generations

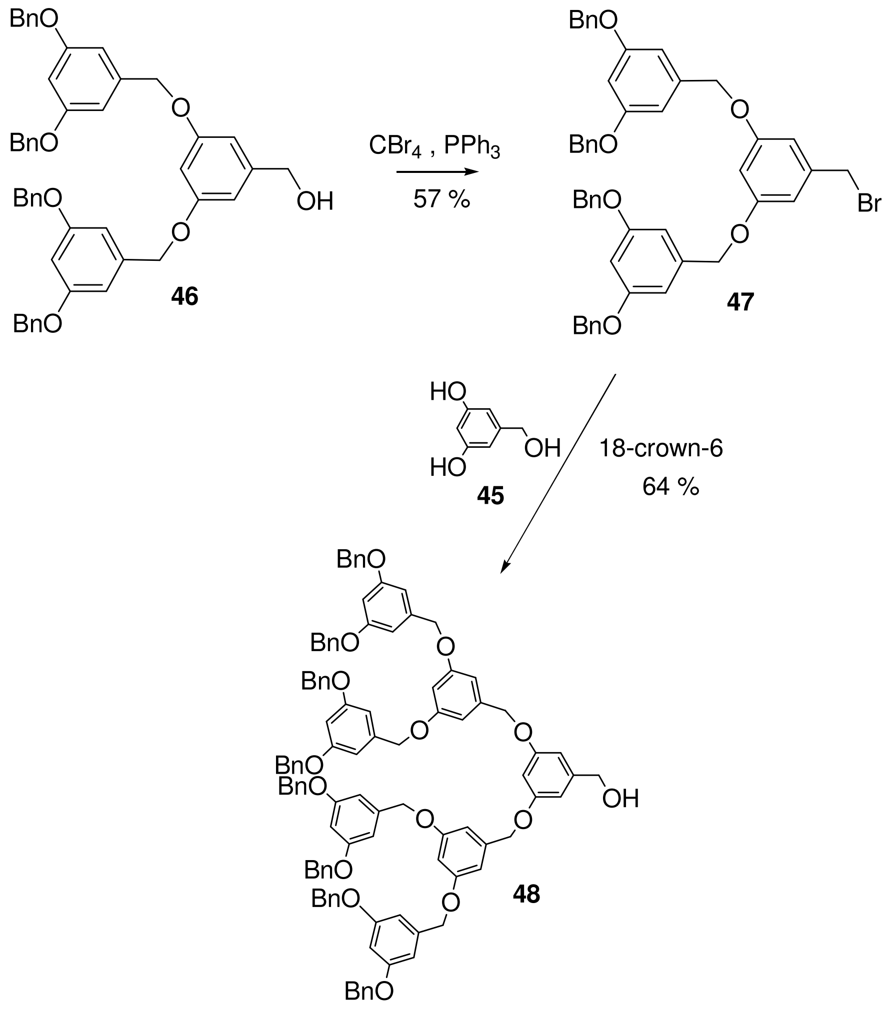


Figure 4.3. Poly (aryl ether) dendron synthesis: Higher generations

4.3.1.1. Synthesis of ethyl-3,5-dihydroxybenzoate. A mixture of 3,5-dihydroxybenzoic acid **39** (10 g, 64.93 mmol), H_2SO_4 (1 mL) and ethanol (150 mL) was refluxed at 70ºC for 24 h under N_2. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and ethyl acetate and the aqueous layer was extracted with ethyl acetate (3 x 25 mL).The combined organic layers were evaporated under *vacuo* to give ethyl-3,5-dihydroxybenzoate **40** as a light yellow crystalline solid (10.64 g, 90 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.08 (d, 2H, *J* = 2.4 Hz), 6.54 (t, 1H, *J* = 2.4 Hz), 4.33 (q, 2H, *J* = 7.2 Hz), 1.36 (t, 3H, *J* = 7.2 Hz) corresponding to the literature values [20] (Figure A.1).

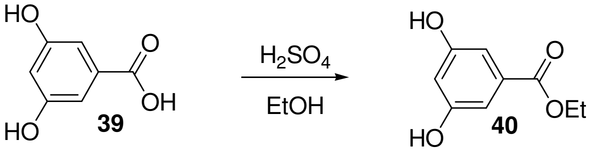


Figure 4.4. Synthesis of ethyl-3,5-dihydroxybenzoate

4.3.1.2. Synthesis of G_1-ester. A mixture of benzyl bromide **41** (7.67 mL, 64.56 mmol), **40** (4.70 g, 25.82 mmol), dried potassium carbonate (8.92 g, 64.56 mmol) and 18-crown-6 (1.36 g, 5.16 mmol) in dry acetone (45 mL) was refluxed at 70°C and stirred for 24 h under N_2. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by recrystallization from hexane:ethyl acetate (3:1) to give G_1-ester **42** as a white crystalline solid (7.68 g, 85 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.43 - 7.30 (m, 10H), 7.29 (d, 2H, *J* = 2.4 Hz), 6.78 (t, 1H, *J* = 2.4 Hz), 5.06 (s, 4H), 4.36 (q, 2H, *J* = 7.2 Hz), 1.39 (t, 3H, *J* = 7.2 Hz) corresponding to the literature values [20] (Figure A.2).

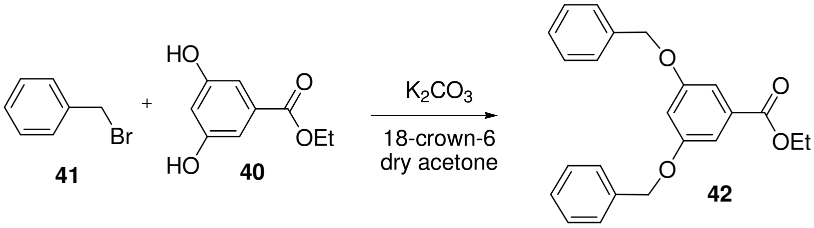


Figure 4.5. Synthesis of G_1-ester

4.3.1.3. Synthesis of G_1-alcohol. To a stirring solution of G_1-ester **40** (6.00 g, 17.14 mmol) in dry THF (95 mL), $LiAlH_4$ (1.95 g, 51.42 mmol) was added very slowly at 0ºC under N_2. The reaction mixture was stirred at room temperature under N_2 for 24 h. Then, water (10.00 mL) was added slowly to decompose the excess $LiAlH_4$ and the solution was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the volatiles were evaporated under *vacuo*. The crude product was filtered through a plug of silica with ethyl acetate as eluent to yield G_1-alcohol **43** as white crystalline solid

(5.25 g, 95 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.42 - 7.28 (m, 10H), 6.61 (d, 2H, *J* = 2.0 Hz), 6.53 (t, 1H, *J* = 2.0 Hz), 5.03 (s, 4H), 4.62 (s, 2H) corresponding to the literature values [20] (Figure A.3).

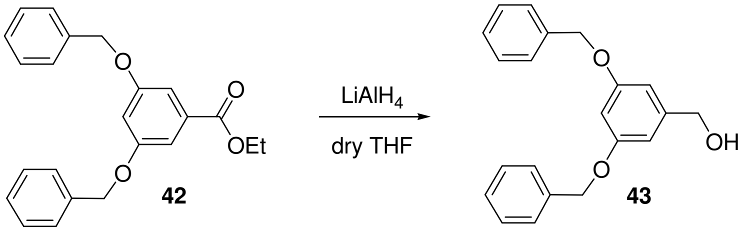


Figure 4.6. Synthesis of G_1-alcohol

4.3.1.4. Synthesis of G_1-bromide. To a stirring mixture of G_1-alcohol **43** (5.00 g, 15.62 mmol), CBr_4 (10.36 g, 31.25 mmol), and dry THF (4 mL) under N_2 was added triphenylphosphine (8.19 g, 31.25 mmol). The reaction mixture was stirred at room temperature under nitrogen for 1.5 h. Then, water (10.00 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. The volatiles were removed under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (1:19) as eluent to obtain G_1-bromide **44** as a white crystalline solid (4.00 g, 67 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.42 - 7.31 (m, 10H), 6.63 (d, 2H, *J* = 2.4 Hz), 6.53 (t, 1H, *J* = 2.4 Hz), 5.01 (s, 4H), 4.40 (s, 2H) corresponding to the literature values [20] (Figure A.4).

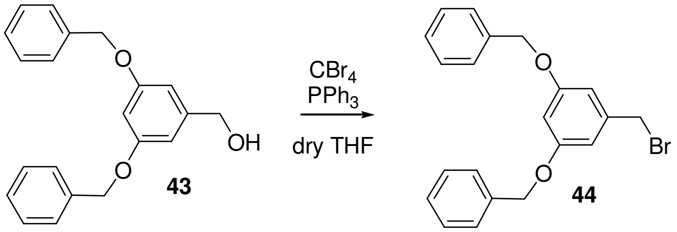


Figure 4.7. Synthesis of G_1-bromide

4.3.1.5. Synthesis of G_2-alcohol. A mixture of G_1-bromide **44** (9.32 g, 24.39 mmol), 3,5-dihydroxybenzyl alcohol (1.55 g, 11.08 mmol), dried potassium carbonate (3.83 g, 27.72

mmol) and 18-crown-6 (0.58 g, 2.2 mmol) in dry acetone (37.00 mL) was refluxed at 70°C and stirred for 48 h under N_2. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (1:3) as eluent to obtain G_2-alcohol **46** as a white crystalline solid (7.10 g, 86 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, 20H), 6.66 (d, 4H, *J* = 2.4 Hz), 6.58 (d, 2H, *J* = 2.4 Hz), 6.55 (t, 2H, *J* = 2.4 Hz), 6.50 (t, 1H, *J* = 2.4 Hz), 5.01 (s, 8H), 4.96 (s, 4H), 4.61 (s, 2H) corresponding to the literature values [8] (Figure A.5).

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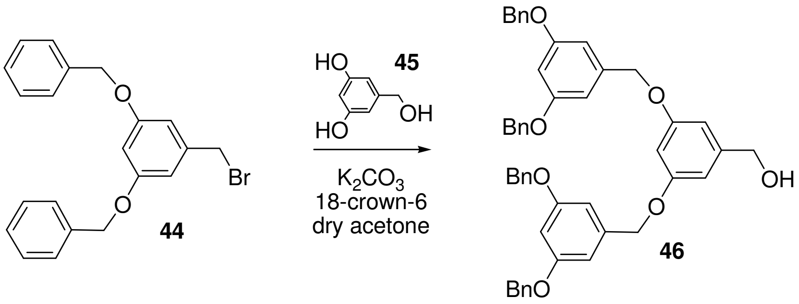


Figure 4.8. Synthesis of G_2-alcohol

4.3.1.6. Synthesis of G_2 bromide. To a stirring mixture of G_2-alcohol **46** (4.50 g, 6.06 mmol), CBr_4 (6.03 g, 18.19 mmol), and dry THF (5.00 mL) under N_2 was added triphenylphosphine (4.77 g, 18.19 mmol). The reaction mixture was stirred at room temperature, under nitrogen for 1.5 h. Then, water (10.00 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were combined and dried with anhydrous Na_2SO_4. The volatiles were removed under *vacuo*. The crude product was purified by column chromatography with CH_2Cl_2:hexane (1:1) as eluent to obtain G_2-bromide **47** as a white crystalline solid (2.78 g, 57 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.40 - 7.30 (m, 20H), 6.65 (d, 4H, *J* = 2.0 Hz), 6.60 (d, 2H, *J* = 2.0 Hz), 6.55 (t, 2H, *J* = 2.0 Hz), 6.49 (t, 1H, *J* = 2.0 Hz), 5.01 (s, 8H), 4.94 (s, 4H), 4.39 (s, 2H) corresponding to the literature values [8] (Figure A.6).

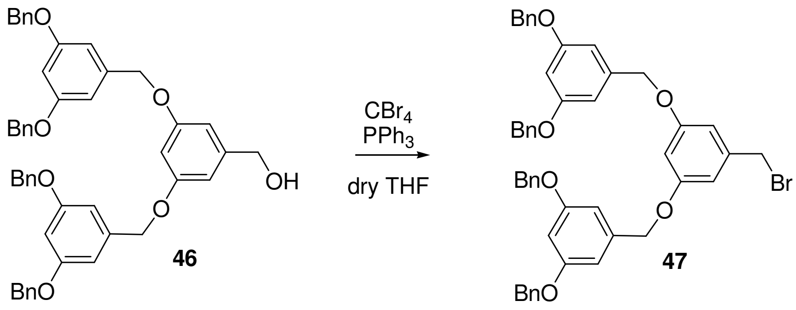


Figure 4.9. Synthesis of G_2-bromide

4.3.1.7. Synthesis of G_3 alcohol. A mixture of G_2-bromide **47** (2.77 g, 3.43 mmol), 3,5-dihydroxybenzyl alcohol (0.21 g, 1.56 mmol), dried potassium carbonate (0.53 g, 3.9 mmol) and 18-crown-6 (0.08 g, 0.31 mmol) in dry acetone (10.00 mL) was refluxed at 70°C and stirred for 48 h under N_2. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:CH_2Cl_2 (1:19) as eluent to obtain G_3-alcohol **48** as a colorless oil (1.59 g, 64 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}HNMR 7.51 - 7.38 (m, 40H), 6.81 - 6.78 (m, 12H), 6.69 - 6.67 (m, 9H), 5.07 (s, 16H), 5.01 (s, 12H), 4.61 (s, 2H) corresponding to the literature values [8] (Figure A.7).

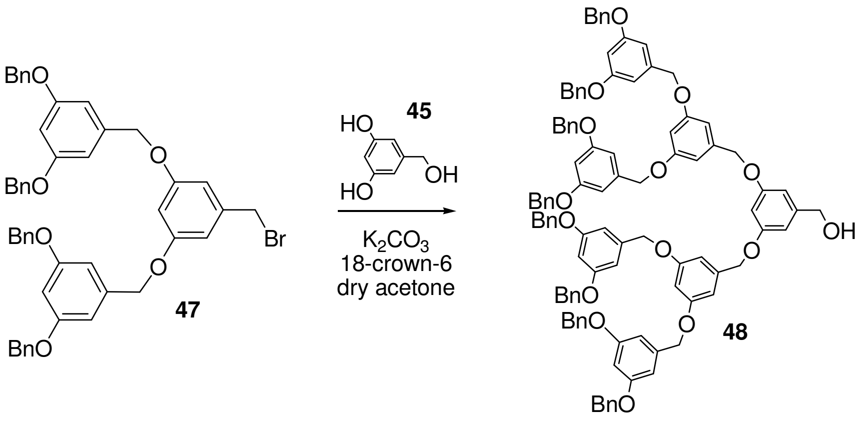


Figure 4.10. Synthesis of G_3-alcohol

4.3.2. Polyether Dendron

Aliphatic polyether dendrons which have benzyl protecting groups are of choice because of their chemical durability towards oxidative, reductive, strongly basic and weakly acidic reaction conditions. This property brings the synthetic chemist to apply a variety of chemical modifications both at the periphery and at the focal point. The benzyl protecting groups can also be removed quantitatively to obtain poly-ol dendrons, which will give the dendron enhanced water solubility because of the hydrophilic groups at the periphery. In this way, dendrons which have a robust nature and aliphatic ether building blocks with tailored solubility properties can be obtained. The synthesis procedure which is outlined here was adopted from a report by Grayson and Fréchet [21].

The synthesis starts with an S_N2 reaction between epichlorohydrin **49** and benzyl alcohol **50** which will become the surface groups of the dendron. Benzyl alcohol **50** is added in excess in order to decrease the formation of the mono substituted product but unfortunately there is always a trace amount left which is later purified by vacuum distillation. At the end of this purification G_1-ol **51** is obtained (Figure 4.11).

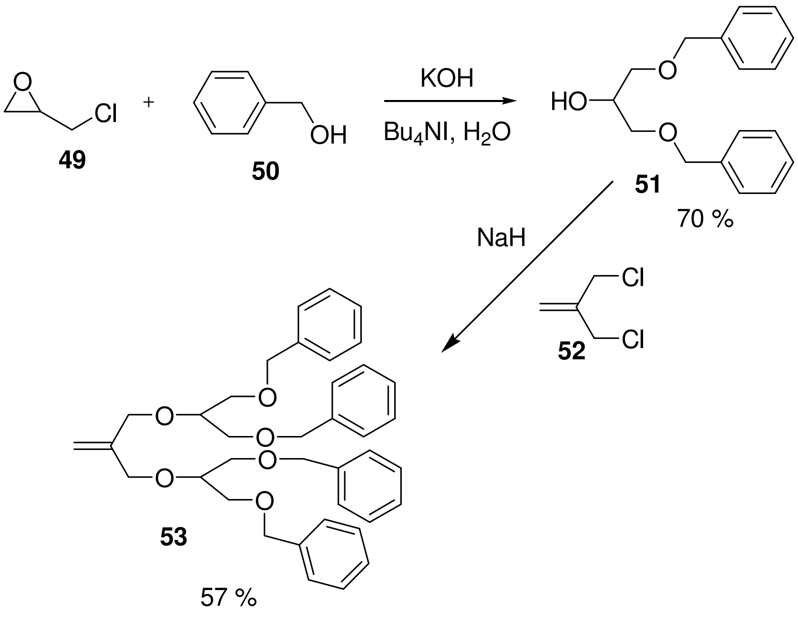


Figure 4.11. Polyether dendron synthesis: Lower generations

Double nucleophilic displacement of the chloride groups of methallyl dichloride with G_1-ol **51** yields G_2-ene **53**. In order to continue to the synthesis of the higher generations the focal point of G_2-ene **53** is activated via a hydroboration/oxidation reaction with BH_3 / H_2O_2 resulting a hydroxyl group at the focal point. The substitution of the chloride group and the hydroboration steps are alternately applied in order to obtain the corresponding G_3-ene **55** and G_3-ol **56** (Figure 4.12).

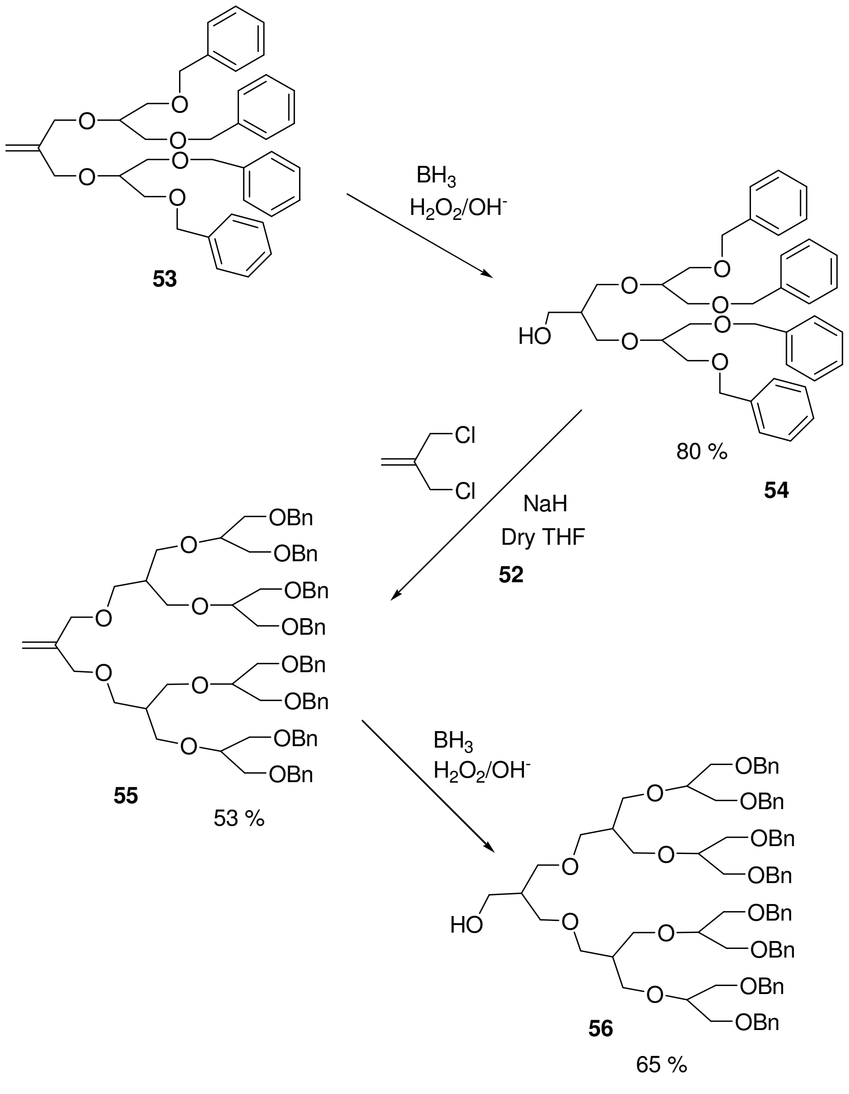


Figure 4.12. Polyether dendron synthesis: Higher generations

As can be seen from the procedure the convergent method is applied for the synthesis of this polyether dendron. An alternating sequence of S_N2 and hydroboration reactions is applied to obtain the dendron. Synthesis steps are explained in detail in subsequent sections.

4.3.2.1. Synthesis of G_1-ol. To a stirring mixture of tetra-n-butylammonium iodide (3.69 g, 0.05 mmol) in benzyl alcohol **50** (20.70 mL, 1.00 mmol) under N_2 was added KOH (8.41 g, 0.75 mmol) followed by the slow addition of epichlorohydrin (3.92 mL, 0.25 mmol). The reaction mixture was refluxed at 65°C for 40 h under N_2. Then, the reaction mixture was allowed to cool to room temperature and was poured into an ice-water mixture. The organic layer was extracted with H_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo.* The crude product was vacuum distilled in order to obtain G_1-ol **51** as a colorless liquid (47.6 mg, 70 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.35 - 7.25 (m, 10H), 4.54 (s, 4H), 4.02 - 4.00 (m, 1H), 3.57 - 3.49 (m, 4H), 2.46 (bs, 1H) corresponding to the literature values [21] (Figure A.8).

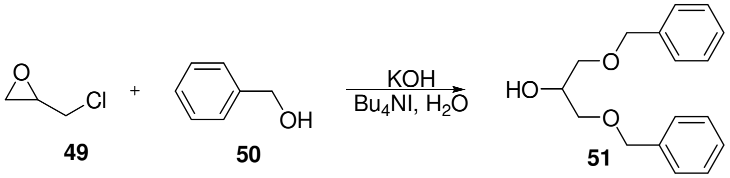


Figure 4.13. Synthesis of G_1-ol

4.3.2.2. Synthesis of G_2-ene. Solid NaH (60 %, 0.80 g, 33.36 mmol) was washed with freshly distilled THF (10.00 mL) at room temperature under N_2 and suspended in THF (25.00 mL). To this slurry was added methallyl dichloride **52** (0.77 mL, 6.67 mmol) followed by the dropwise addition of G_1-ol **51** (5.00 g, 18.35 mmol). The reaction mixture was stirred at room temperature for 15 minutes and then, refluxed at 65ºC for 12 h under N_2. Then, the reaction mixture was allowed to cool to room temperature and water (5 mL) was added to decompose the excess NaH. Aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (3:17) as eluent to obtain G_2-ene **53** as a colorless oil (2.26 g, 57 %

yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 - 7.24 (m, 20H), 5.17 (s, 2H), 4.49 (s, 8H), 4.14 (s, 4H), 3.71 - 3.66 (m, 2H), 3.59 - 3.51 (m, 8H) corresponding to the literature values [21] (Figure A.9).

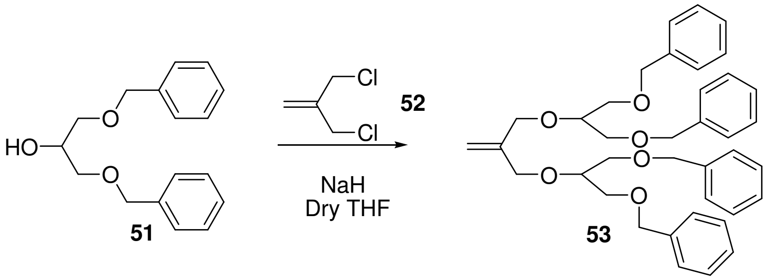


Figure 4.14. Synthesis of G_2-ene

<u>4.3.2.3. Synthesis of G_2-ol.</u> A stirring mixture of G_2-ene **53** (2.10 g, 3.52 mmol) in THF (5.00 mL) was cooled in a salt-ice bath followed by the dropwise addition of 1.0 M BH_3 (7.03 mL, 7.03 mmol) under N_2. The reaction mixture was stirred for 2 h under N_2 below 0°C. After warming up the reaction mixture to room temperature, 3.0 M NaOH solution (4.6 mL, 14.00 mmol) was added and the reaction mixture was stirred for an additional 15 min. Then, H_2O_2 (30 %, 1.04 mL, 10.56 mmol) was added and the reaction mixture was stirred for 45 min at room temperature. Then, the aqueous layer was extracted with ethyl acetate (3 x 25 mL), dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (1:3) as eluent to obtain G_2-ol **54** as a colorless oil (1.73 g, 80 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.33 - 7.25 (m, 20H), 4.49 (s, 8H), 3.74 - 3.62 (m, 8H), 3.55 - 3.47 (m, 8H), 2.11 - 2.06 (m, 1H), 2.01 (bs, 1H) corresponding to the literature values [21] (Figure A.10).

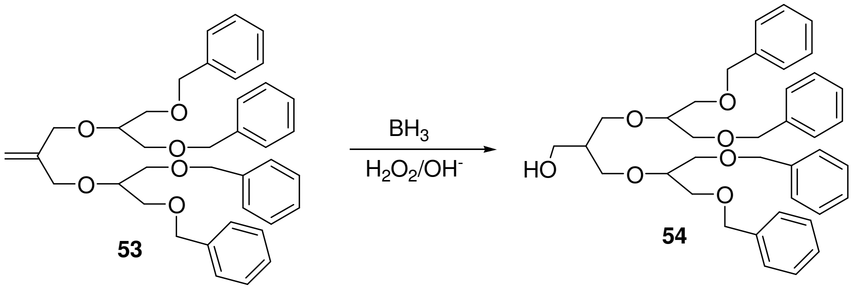


Figure 4.15. Synthesis of G_2-ol

4.3.2.4. Synthesis of G_3-ene. Solid NaH (60 %, 0.05 g, 2.30 mmol) was washed with freshly distilled THF (10.00 mL) at room temperature under N_2 and suspended in THF (5.00 mL). To this slurry was added methallyl dichloride **52** (0.05 mL, 0.46 mmol) followed by the dropwise addition of G_2-ol **54** (0.78 g, 1.26 mmol). The reaction mixture was stirred at room temperature for 15 minutes and then, refluxed at 65ºC for 12 h under N_2. Then, the reaction mixture was allowed to cool to room temperature and water (5 mL) was added to decompose the excess NaH. Aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (1:4) as eluent to obtain G_3-ene **55** as a colorless oil (0.31 g, 53 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 - 7.20 (m, 40H), 5.06 (s, 2H), 4.48 (s, 16H), 3.85 (s, 4H), 3.63 - 3.44 (m, 32H), 2.18 - 2.15 (m, 2H) corresponding to the literature values [21] (Figure A.11).

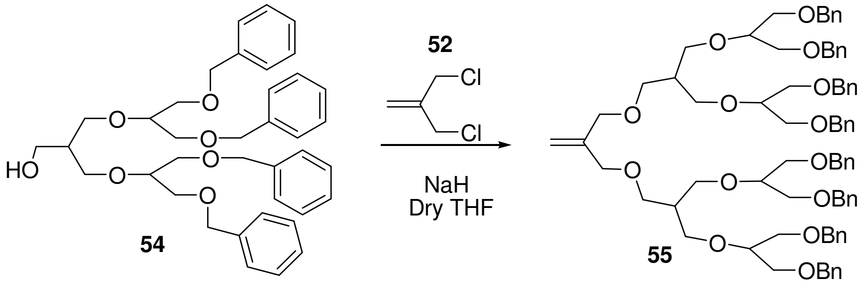


Figure 4.16. Synthesis of G_3-ene

4.3.2.5. Synthesis of G_3-ol. A stirring mixture of G_3-ene **55** (0.8 g, 0.624 mmol) in THF (5.00 mL) was cooled in a salt-ice bath followed by the dropwise addition of 1.0 M BH_3 (1.24 mL, 1.24 mmol) under N_2. The reaction mixture was stirred for 2 h under N_2 below 0°C. After warming up the reaction mixture to room temperature 3.0 M NaOH (0.93 mL, 2.80 mmol) was added and the reaction mixture was stirred for an additional 15 min. Then, H_2O_2 (0.14 mL, 1.87 mmol) was added and the reaction mixture was stirred for 45 min at room temperature. Then, the aqueous layer was extracted with ethyl acetate (3 x 25 mL), dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (3:7) as eluent to obtain G_3-ol **56** as a colorless oil (0.51 g, 65 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.29 - 7.22

(m, 40H), 4.48 (s, 16H), 3.63 - 3.30 (m, 39H), 2.18 - 2.12 (m, 2H), 2.03 – 2.01 (m, 1H) corresponding to the literature values [21] (Figure A.12).

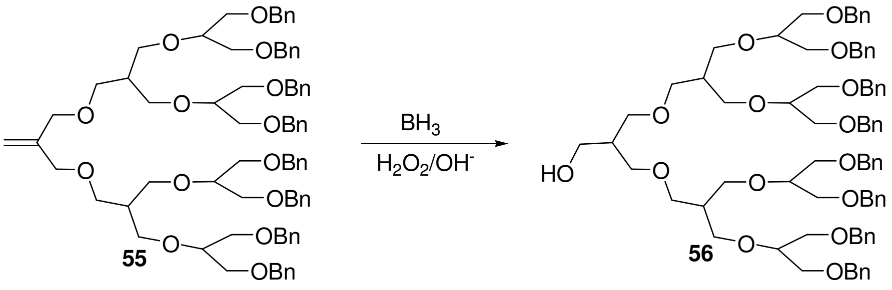


Figure 4.17. Synthesis of G_3-ol

4.4. Functionalization of Dendrons

4.4.1. Functionalization of Poly (aryl) ether Dendrons

In order to synthesize nonsymmetrical dendrimers using click chemistry, modification of the dendrons are required. G_1, G_2 and G_3-alcohol dendrons are functionalized with azide and alkyne moieties to participate in the copper (II) catalyzed click reactions.

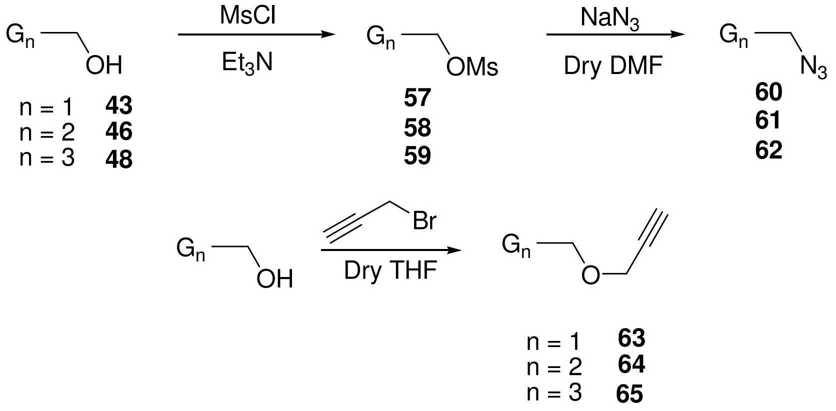


Figure 4.18. Functionalization of G_1, G_2, G_3-alcohol dendrons

The azide functionalized dendrons were prepared by first converting the G_1, G_2 and G_3-alcohols in to the corresponding mesylates **57**-**59** and then, the reaction of these mesylates with NaN_3 in the presence of dry DMF yielded in G_1, G_2 and G_3-azides **60-62**.

The acetylene functionalized dendrons **63-65** were prepared by reacting G_1, G_2 and G_3-alcohols with propargyl bromide in the presence of NaH and dry THF.

4.4.1.1. Synthesis of G_1-mesylate. To a stirring mixture of G_1-alcohol **43** (3.00 g, 3.37 mmol) and Et_3N (2.59 mL, 18.75 mmol) in dry CH_2Cl_2 (90 mL) under N_2 was added methanesulfonyl chloride (1.45 mL, 18.75 mmol). The reaction mixture was stirred at room temperature under N_2 for 12 h. Then, the reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo* to obtain G_1-mesylate **57** as a yellow oil (3.5 g, 100 % yield).

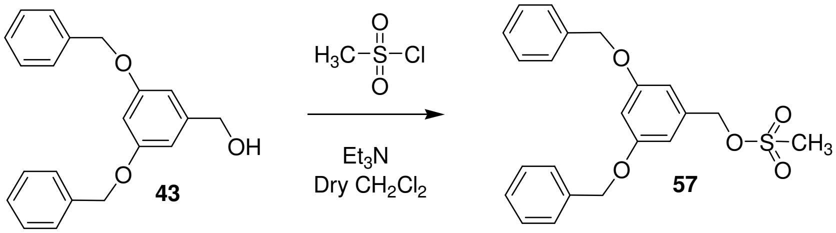


Figure 4.19. Synthesis of G_1-mesylate

4.4.1.2. Synthesis of G_1-azide. To a stirring solution of G_1-mesylate **57** (1.50 g, 3.98 mmol) in dry DMF (19.9 mL) under N_2 was added NaN_3 (0.38 g, 5.98 mmol). The reaction mixture was refluxed at 55°C under N_2 for 16 h. Then, the reaction mixture was partitioned between water and a mixture of ethyl acetate:hexane (1:1) and the organic layer was extracted with water (3 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was filtered through a plug of silica with ethyl acetate as eluent to obtain G_1-azide **60** as a yellow oil (1.36 g, 99 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.42 - 7.32 (m, 10H), 6.58 (t, 1H, J = 2.4 Hz), 6.55 (d, 2H, J = 2.4 Hz), 5.03 (s, 4H), 4.26 (s, 2H) corresponding to the literature values [22] (Figure A.13).

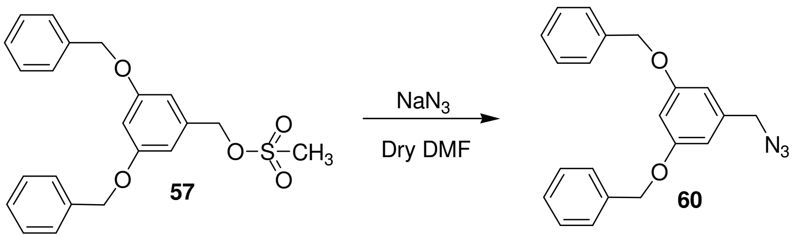


Figure 4.20. Synthesis of G_1-azide

4.4.1.3. Synthesis of G_2-mesylate. To a stirring mixture of G_2-alcohol **46** (0.742 g, 1.00 mmol) and Et_3N (0.27 mL, 2mmol) in dry CH_2Cl_2 (25 mL) under N_2 was added methanesulfonyl chloride (0.15 mL, 2 mmol). The reaction mixture was stirred at room temperature under N_2 for 12 h. Then, the reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo* to obtain G_2-mesylate **58** as a yellow oil (0.82 g, 100 % yield).

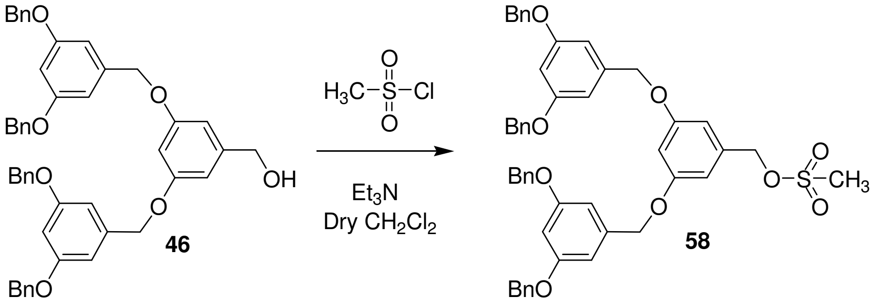


Figure 4.21. Synthesis of G_2-mesylate

4.4.1.4. Synthesis of G_2-azide. To a stirring solution of G_2-mesylate **58** (0.95 g, 1.28 mmol) in dry DMF (12.7 mL) under N_2 was added NaN_3 (0.12 g, 1.93 mmol). The reaction mixture was refluxed at 55°C under N_2 for 16 h. Then, the reaction mixture was partitioned between water and a mixture of ethyl acetate:hexane (1:1) and the organic layer was extracted with water (3 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was filtered through a plug of silica with ethyl acetate as eluent to obtain G_2-azide **61** as a yellow solid (0.62 g, 64 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41 - 7.30 (m, 20H), 6.66 (d, 4H, J = 2.4 Hz), 6.56 (t, 2H, J

= 2.4 Hz), 6.52 – 6.51 (m, 3H), 5.01 (s, 8H), 4.96 (s, 4H), 4.24 (s, 2H) corresponding to the literature values [22] (Figure A.14).

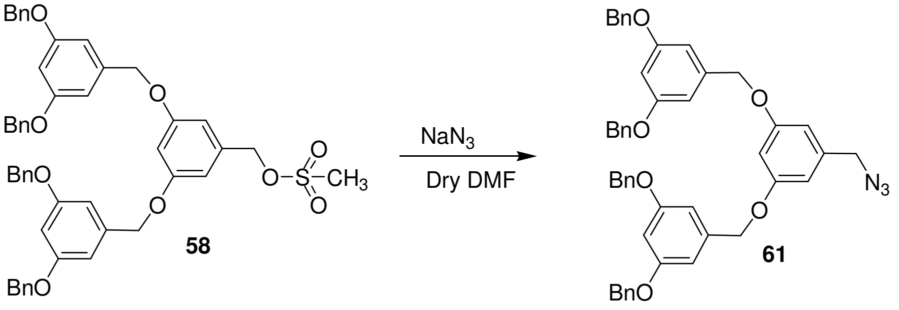


Figure 4.22. Synthesis of G_2-azide

4.4.1.5. Synthesis of G_3-mesylate. To a stirring mixture of G_3-alcohol **48** (0.76 g, 0.47 mmol) and Et_3N (0.13 mL, 0.95 mmol) in dry CH_2Cl_2 (6.00 mL) under N_2 was added methanesulfonyl chloride (0.74 mL, 0.95 mmol). The reaction mixture was stirred at room temperature under N_2 for 12 h. Then, the reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo* to obtain G_3-mesylate **59** as a yellow oil (0.73 g, 97 % yield).

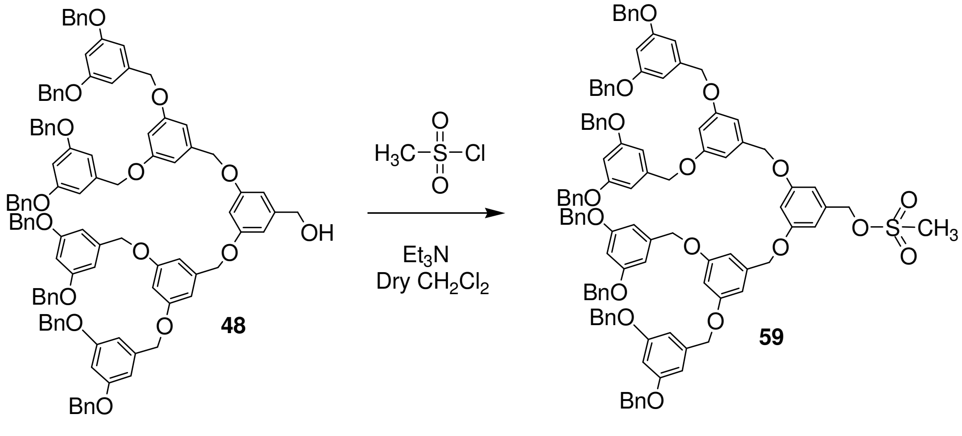


Figure 4.23. Synthesis of G_3-mesylate

4.4.1.6. Synthesis of G_3-azide. To a stirring solution of G_3-mesylate **59** (0.73 g, 0.43 mmol) in dry DMF (4.00 mL) under N_2 was added NaN_3 (0.08 g, 1.31 mmol). The reaction mixture was refluxed at 55°C under N_2 for 16 h. Then, the reaction mixture was partitioned between water and a mixture of ethyl acetate:hexane (1:1) and the organic layer was extracted with water (3 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was filtered through a plug of silica with ethyl acetate as eluent to obtain G_3-azide **62** as a yellow oil (0.67 g, 95 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 40H), 6.72 - 6.70 (m, 12H), 6.61 - 6.57 (m, 9H), 5.03 (s, 16H), 4.98 (s, 12H), 4.24 (s, 2H) corresponding to the literature values [22] (Figure A.15).

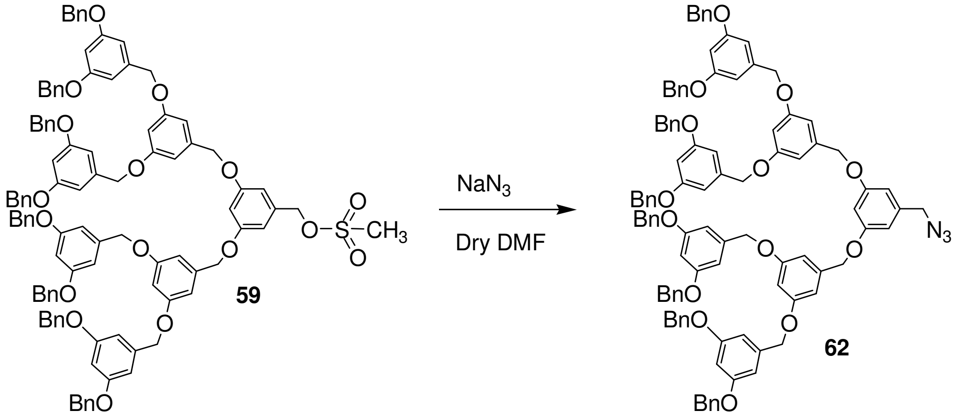


Figure 4.24. Synthesis of G_3-azide

4.4.1.7. Synthesis of G_1-acetylene. Solid NaH (60 %, 0.24 g, 10.00 mmol) was washed with freshly distilled THF (5 mL) at room temperature under N_2 and dissolved in THF (5 mL). To this slurry was added G_1-alcohol **43** (0.64 g, 2.00 mmol) followed by the slow addition of propargyl bromide (80 %, 0.43 mL, 5.00 mmol). The reaction mixture was refluxed at 65°C for 15 h. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (1:9) as eluent to obtain G_1-acetylene **63** as a colorless oil (0.60 g, 85 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, 10H), 6.60 (d, 2H, *J* = 2.4 Hz), 6.54 (t, 1H, *J* = 2.4 Hz), 5.02 (s, 4H), 4.53 (s, 2H), 4.14 (d, 2H, *J* = 2.4 Hz), 2.43 (t, 1H *J* = 2.4 Hz), corresponding to the literature values [23] (Figure A.16).

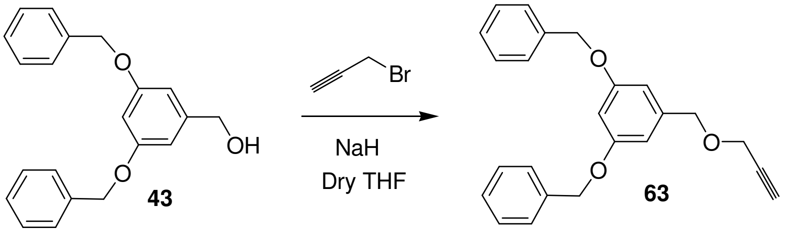


Figure 4.25. Synthesis of G_1-acetylene

4.4.1.8. Synthesis of G_2-acetylene. Solid NaH (60 %, 0.80 g, 3.36 mmol) was washed with freshly distilled THF (5 mL) at room temperature under N_2 and dissolved in THF (5 mL). To this slurry was added G_2-alcohol **46** (0.50 g, 0.67 mmol) followed by the slow addition of propargyl bromide (80 %, 0.14 mL, 1.68 mmol). The reaction mixture was refluxed at 65°C for 15 h. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (1:3) as eluent to obtain G_2-acetylene **64** as a colorless oil (0.39 g, 77 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, 20H), 6.66 (d, 4H, *J* = 2.0 Hz), 6.59 (d, 2H, *J* = 2.0 Hz), 6.55 (t, 2H, *J* = 2.0 Hz), 6.51 (t, 1H, *J* = 2.0 Hz), 5.02 (s, 8H), 4.95 (s, 4H), 4.53 (s, 2H), 4.14 (d, 2H, *J* = 2.4 Hz), 2.44 (t, 1H, *J* = 2.0 Hz) corresponding to the literature values [23] (Figure A.17).

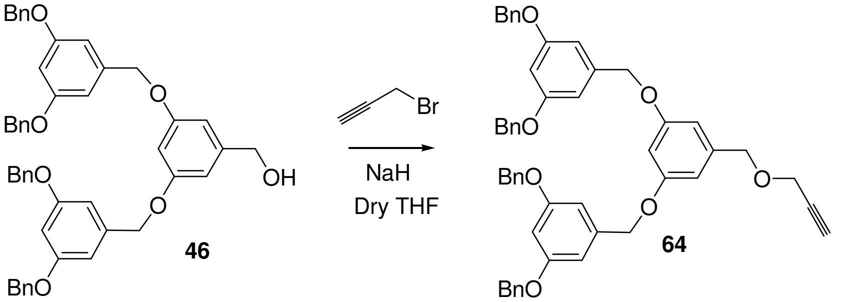


Figure 4.26. Synthesis of G_2-acetylene

4.4.1.9. Synthesis of G_3-acetylene. Solid NaH (60 %, 0.01 g, mmol) was washed with freshly distilled THF (5 mL) at room temperature under N_2 and dissolved in THF (0.12 mL). To this slurry was added G_3-alcohol **48** (0.15 g, 0.09 mmol) followed by the slow addition of propargyl bromide (80 %, 0.02 mL, mmol). The reaction mixture was refluxed at 65°C for 15 h. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (2:3) as eluent to obtain G_3-acetylene **65** as a colorless oil (0.10 g, 70 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 40H), 6.72 – 6.70 (m, 13H), 6.66 (d, 2H, $J = 2.0$ Hz), 6.61 (t, 4H, $J = 2.0$ Hz), 6.62 (t, 2H, $J = 2.0$ Hz), 5.04 (s, 16H), 4.98 (s,12H), 4.57 (s, 2H), 4.18 (d, 2H, $J = 2.0$ Hz), 2.47 (t, 1H, $J = 2.0$ Hz) corresponding to the literature values [23] (Figure A.18).

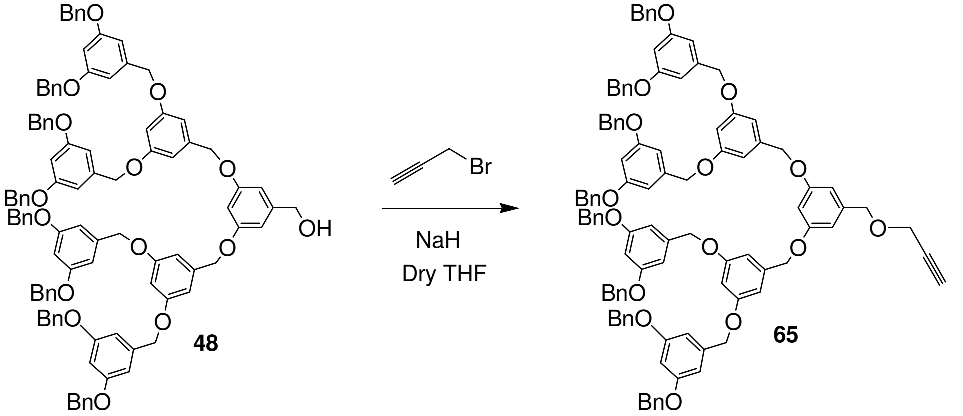


Figure 4.27. Synthesis of G_3-acetylene

4.4.2. Functionalization of Polyether Dendrons

The azide functionalized dendrons were prepared by first converting the G_1, G_2 and G_3-ols in to the corresponding mesylates **66-68** and then, the reaction of these mesylates with NaN_3 in the presence of dry DMSO yielded in G_1, G_2 and G_3-azides **69-71**.

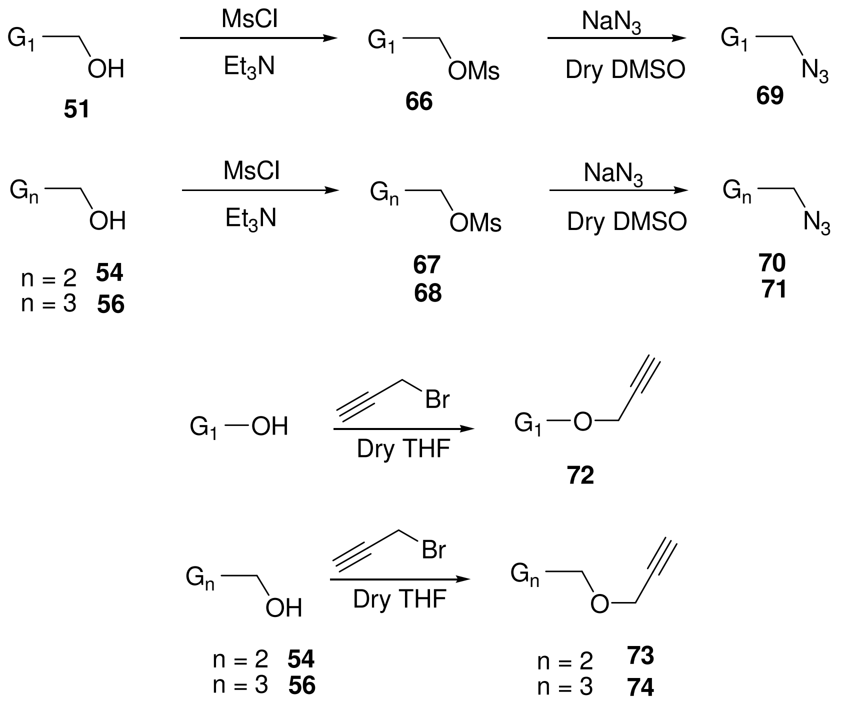


Figure 4.28. Functionalization of G_1, G_2, G_3-ol dendrons

The acetylene functionalized dendrons **72**-**74** were prepared by reacting G_1, G_2 and G_3-ols with propargyl bromide in the presence of NaH and dry THF.

4.4.2.1. Synthesis of G_1-mesylate. To a stirring mixture of G_1-ol **51** (0.40 g, 1.47 mmol) and Et_3N (0.41 mL, 2.94 mmol) in dry CH_2Cl_2 (15.00 mL) under N_2 was added methanesulfonyl chloride (0.23 mL, 2.94 mmol). The reaction mixture was stirred at room temperature under N_2 for 12 h. Then, the reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo* to obtain G_1-mesylate **66** as a yellow oil (0.47 g, 91 % yield).

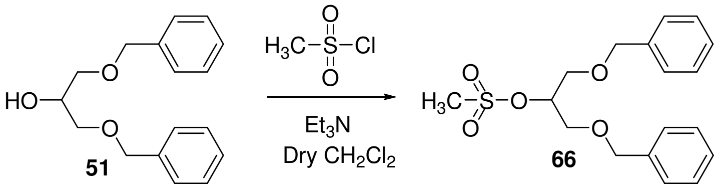


Figure 4.29. Synthesis of G_1-mesylate

4.4.2.2. Synthesis of G_1-azide. To a stirring solution of G_1-mesylate **66** (0.46 g, 1.34 mmol) in dry DMSO (3.00 mL) under N_2 was added NaN_3 (0.17 g, 2.68 mmol). The reaction mixture was refluxed at 70°C under N_2 for 12 h. Then, the reaction mixture was partitioned between water and a mixture of ethyl acetate and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was filtered through a plug of silica with ethyl acetate as eluent to obtain G_1-azide **69** a yellow oil (0.29 g, 75 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) 7.35 - 7.25 (m, 10H), 4.53 (s, 4H), 3.77 - 3.69 (m, 1H), 3.63 - 3.54 (m, 4H) corresponding to the literature values [24] (Figure A.19)

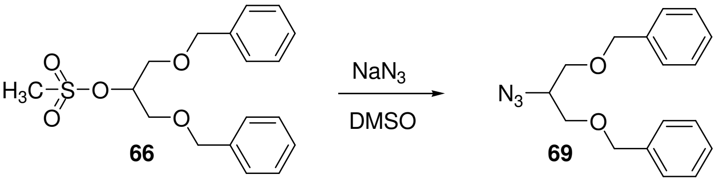


Figure 4.30. Synthesis of G_1-azide

4.4.2.3. Synthesis of G_2-mesylate. To a stirring mixture of G_2-ol **54** (0.74 g, 1.20 mmol) and Et_3N (0.33 mL, 2.40 mmol) in dry CH_2Cl_2 (15.00 mL) under N_2 was added methanesulfonyl chloride (0.18 mL, 2.40 mmol). The reaction mixture was stirred at room temperature under N_2 for 12 h. Then, the reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo* to obtain G_2-mesylate **67** as a yellow oil (0.79 g, 94 % yield).

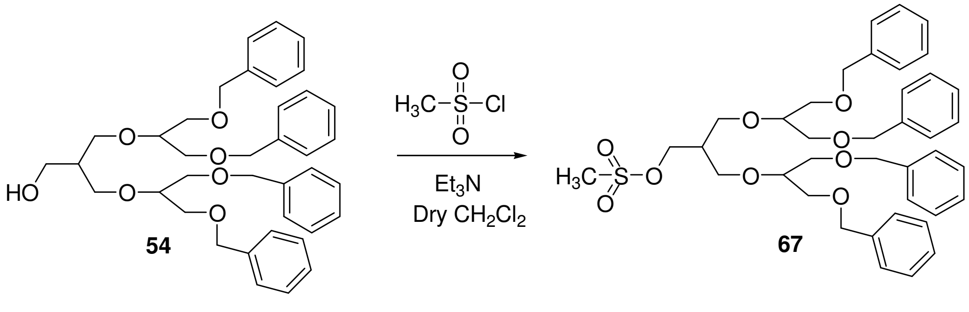


Figure 4.31. Synthesis of G_2-mesylate

4.4.2.4. Synthesis of G_2-azide. To a stirring solution of G_2-mesylate **67** (1.13 g, 1.64 mmol) in dry DMSO (3 mL) under N_2 was added NaN_3 (0.21 g, 3.28 mmol). The reaction mixture was refluxed at 70ºC under N_2 for 12 h. Then, the reaction mixture was partitioned between water and a mixture of ethyl acetate and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was filtered through a plug of silica with ethyl acetate as eluent to obtain G_2-azide **70** a yellow oil (0.94 g, 90 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.28 - 7.17 (m, 20H), 4.45 (s, 8H), 3.62 - 3.46 (m, 14H), 3.39 (d, 2H, *J* = 6.0 Hz), 2.09 (t quintet, 1H, *J* = 6.0, 6.0 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 128.0, 127.24, 127.22, 78.3, 73.1, 70.0, 68.4, 50.1, 40.4 (Figure A.20, A.21).

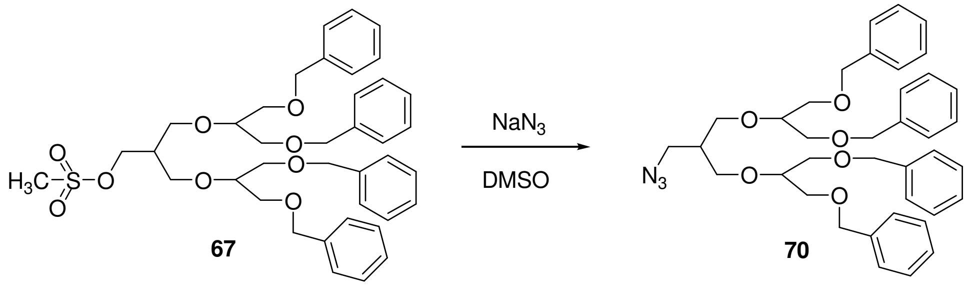


Figure 4.32. Synthesis of G_2-azide

4.4.2.5. Synthesis of G_3-mesylate. To a stirring mixture of G_3-ol **56** (1.00 g, 0.77 mmol) and Et_3N (0.21 mL, 1.54 mmol) in dry CH_2Cl_2 (10 mL) under N_2 was added methanesulfonyl chloride (0.12 mL, 1.54 mmol). The reaction mixture was stirred at room temperature under N_2 for 12 h. Then, the reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo* to obtain G_3-mesylate **68** as a yellow oil (0.92 g, 90 % yield).

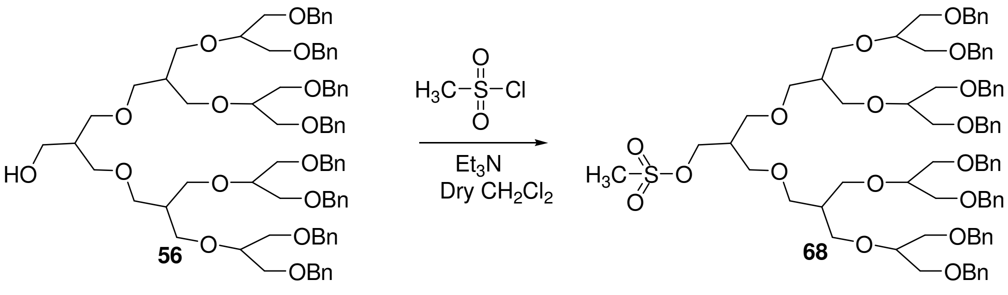


Figure 4.33. Synthesis of G_3-mesylate

<u>4.4.2.6. Synthesis of G_3-azide.</u> To a stirring solution of G_3-mesylate **68** (0.32 g, 0.23 mmol) in dry DMSO (3.00 mL) under N_2 was added NaN_3 (0.03 g, 0.46 mmol). The reaction mixture was refluxed at 70°C under N_2 for 12 h. Then, the reaction mixture was partitioned between water and a mixture of ethyl acetate and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was filtered through a plug of silica with ethyl acetate as eluent to obtain G_3-azide **71** a yellow oil (0.24 g, 83 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.33 - 7.23 (m, 40H), 4.50 (s, 16H), 3.70 – 3.52 (m, 36H), 3.43 (d, 2H, *J* = 6.0 Hz), 2.29 – 2.24 (m, 1H), 2.13 – 2.08 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.3, 127.6, 127.5, 78.5, 73.4, 70.1, 68.6, 68.3, 50.2, 43.7, 42.4, 40.5 (Figure A.22, A.23).

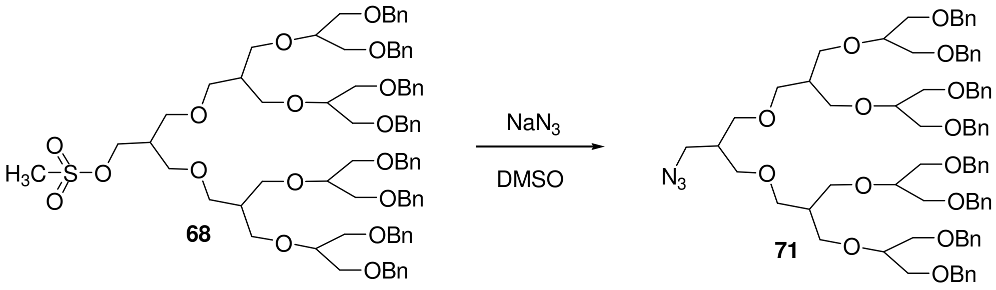


Figure 4.34. Synthesis of G_3-azide

4.4.2.7. Synthesis of G_1-acetylene. Solid NaH (60 %, 0.44 g, 18.35 mmol) was washed with freshly distilled THF (5 mL) at room temperature under N_2 and dissolved in THF (5 mL). To this slurry was added G_1-ol **51** (1.00 g, 3.67 mmol) followed by the slow addition of propargyl bromide (80 %, 0.79 mL, 9.18 mmol). The reaction mixture was refluxed at 65°C for 15 h. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (1:9) as eluent to obtain G_1-acetylene **72** as a colorless oil (1.01 g, 89 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.34 - 7.26 (m, 10H), 4.54 (s, 4H), 4.34 (d, 2H, J = 2.4 Hz), 3.94 (tt, 1H, J = 5.2, 5.2 Hz), 3.65 - 3.58 (m, 4H), 2.40 (t, 1H, J = 2.4 Hz) corresponding to the literature values [25] (Figure A.24).

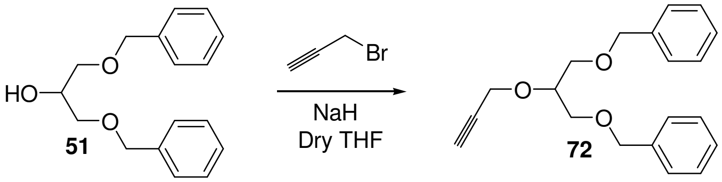


Figure 4.35. Synthesis of G_1-acetylene

4.4.2.8. Synthesis of G_2-acetylene. Solid NaH (60 %, 0.195 g, 8.13 mmol) was washed with freshly distilled THF (5 mL) at room temperature under N_2 and dissolved in THF (5 mL). To this slurry was added G_2-ol **54** (1.00 g, 1.62 mmol) followed by the slow addition of propargyl bromide (80 %, 0.35 mL, 4.06 mmol). The reaction mixture was refluxed at 65°C for 15 h. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (1:9) as eluent to obtain G_2-acetylene **73** as a colorless oil (0.90 g, 86 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 - 7.25 (m, 20H), 4.51 (s, 8H), 4.05 (d, 2H, J = 2.4 Hz), 3.65 - 3.52 (m, 16 H), 2.32 (t, 1H, J = 2.4 Hz), 2.18 (t quintet, 1H, J = 6.0, 6.0 Hz) (Figure A.25).

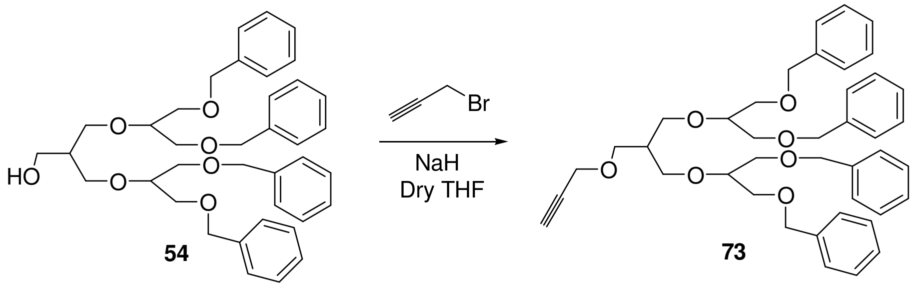


Figure 4.36. Synthesis of G_2-acetylene

4.4.2.9. Synthesis of G_3-acetylene. Solid NaH (60 %, 0.028 g, 1.15 mmol) was washed with freshly distilled THF (5 mL) at room temperature under N_2 and dissolved in THF (5 mL). To this slurry was added G_3-ol **56** (0.30 g, 0.231 mmol) followed by the slow addition of propargyl bromide (80 %, 0.049 mL, 0.57 mmol). The reaction mixture was refluxed at 65°C for 15 h. The mixture was allowed to cool to room temperature and evaporated to dryness under *vacuo*. The residue was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (3:22) as eluent to obtain G_3-acetylene **74** as a colorless oil (0.26 g, 90 % yield). 7.30 – 7.24 (m, 40H), 4.48 (s, 16H), 4.01 (bs, 2H), 3.60 – 3.34 (m, 38H), 2.36 (bs, 1H), 2.14 – 2.07 (m, 3H) (Figure A.26).

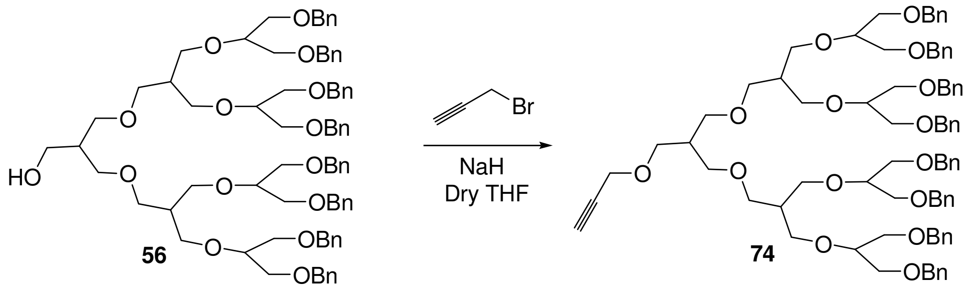


Figure 4.37. Synthesis of G_3-acetylene

4.5. Coupling Reactions of Dendrons

Having the azide and alkyne functionalized dendrons at hand, coupling reactions in the presence of $Cu.SO_4.5H_2O$ and Na ascorbate both at room temperature and at 55ºC were attempted. Since AB type of dendrimers are synthesized for the sake of simplicity, A_1, A_2, A_3 for the poly (aryl) ether dendron and B_1, B_2, B_3 for the polyether dendron will be used. In this way, the corresponding generations of azides and alkynes can clearly be represented for the coupling reactions.

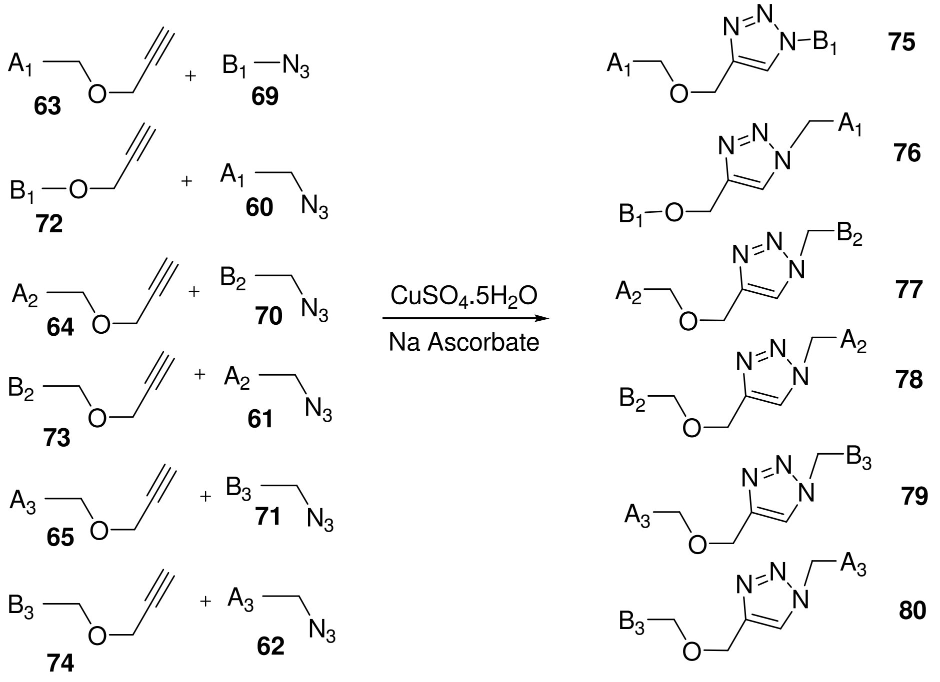


Figure 4.38. Coupling of functionalized dendrons

4.5.1. General Procedure: Coupling of A_1-acetylene with B_1-azide-room temperature

To a stirring solution of A_1-acetylene **63** (30.0 mg, 0.083 mmol) and B_1-azide **69** (27.0 mg, 0.087 mmol) at room temperature in THF:H_2O (1:1) was added a 1.0 M solution of sodium ascorbate in H_2O (0.041 mL, 0.041 mmol) followed by the addition of a 0.3 M solution of $CuSO_4.5H_2O$ in H_2O (0.014 mL, 0.0041 mmol). The reaction mixture was stirred at room temperature for 24 h. Then, THF was removed under *vacuo* and the residue was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over

Na_2SO_4, filtered and the volatiles were removed under *vacuo*. The crude product was purified by column chromatography with ethyl acetate:hexane (2:3) as eluent to obtain A_1-B_1 **75** as a colorless oil (0.045 g, 80 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.40 – 7.18 (m, 20H), 6.61 (d, 2H, *J* = 2.4, 2.4 Hz), 6.54 (t, 1H, *J* = 2.4, 2.4Hz), 5.00 (s, 4H), 4.94 (tt, 1H, *J* = 5.6, 5.6 Hz), 4.66 (s, 2H), 4.53 (s, 2H), 4.47 (dt, 4H, *J* = 12.0, 1.6 Hz), 3.89 (ddt, 4H, *J* = 10.4 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 144.6, 140.4, 137.3, 136.9, 128.52, 128.46, 127.91, 127.89, 127.6, 127.5, 122.9, 106.8, 101.5, 73.4, 72.3, 70.1, 68.8, 63.7, 60.8 (Figure A.27,A.28).

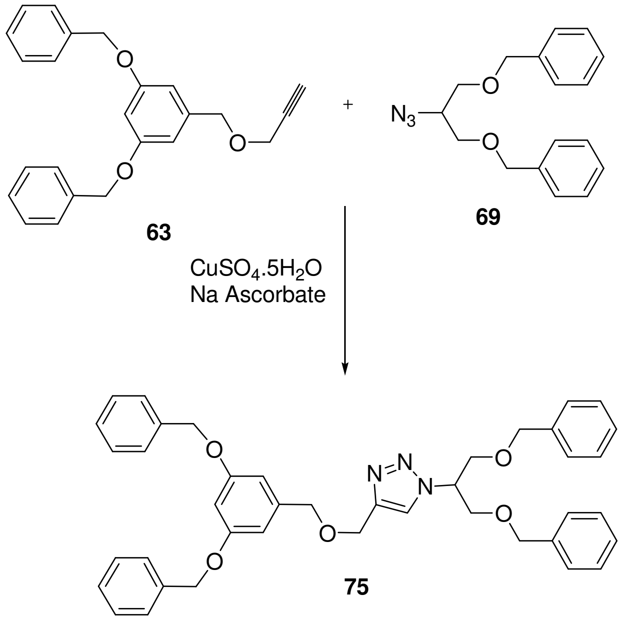


Figure 4.39. Coupling of A_1-acetylene with B_1-azide

4.5.2. Coupling of A_1-acetylene with B_1-azide-55°C

Prepared from A_1-acetylene **63** (31.60 mg, 0.088 mmol) and B_1-azide **69** (28.50 mg, 0.090 mmol) at 55°C according to the general procedure. The crude product was purified by column chromotography with ethyl acetate:hexane (2:3) as eluent to obtain A_1-B_1 **75** as a colorless oil (46.0 mg, 78 % yield).

4.5.3. Coupling of B_1-acetylene with A_1-azide-room temperature

Prepared from B_1-acetylene **72** (0.025 g, 0.081 mmol) and A_1-azide **60** (30 mg, 0.089 mmol) at room temperature according to the general procedure. The crude product was purified by column chromotography with ethyl acetate:hexane (2:3) as eluent to obtain B_1-A_1 **78** as a colorless oil (0.026 g, 50 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.36- 7.24 (m, 20H), 6.56 (t, 1H, J = 2.0, 2.0 Hz), 6.44 (d, 2H, J = 2.0 Hz), 5.32 (s, 2H), 4.96 (s, 4H), 4.81 (s, 2H), 4.49 (s, 4H), 3.85 - 3.83 (m, 1H), 3.63 – 3.56 (m, 4H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 146.0, 138.1, 136.5, 136.4, 128.6, 128.3, 128.1, 127.62, 127.60, 127.5, 122.7, 107.2, 102.1, 77.6, 73.3, 70.18, 70.15, 63.8, 54.2 (Figure A.29, A.30).

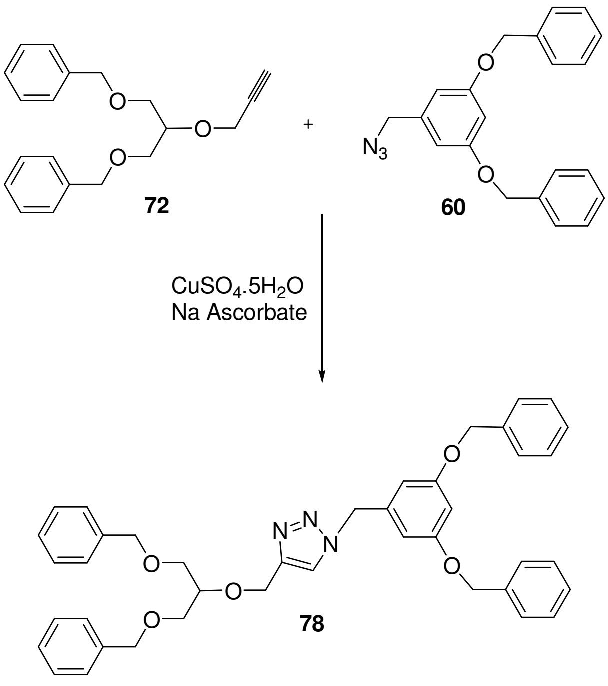


Figure 4.40. Coupling of B_1-acetylene with A_1-azide

4.5.4. Coupling of B_1-acetylene with A_1-azide-55°C

Prepared from B_1-acetylene **72** (25 mg, 0.0805 mmol) and A_1-azide **60** (30 mg, 0.089 mmol) at 55°C according to the general procedure. The crude product was purified by column chromotography with ethyl acetate:hexane (2:3) as eluent to obtain B_1-A_1 **78** as a colorless oil (0.043 g, 82 % yield).

4.5.5. Coupling of A_2-acetylene with B_2-azide-room temperature

Prepared from A_2-acetylene **64** (0.049 g, 0.062 mmol) and B_2-azide **70** (0.042 g, 0.066 mmol) at room temperature according to the general procedure. The crude product was purified by column chromotography with ethyl acetate:hexane (1:1) as eluent to obtain A_2-B_2 **76** as a colorless oil (0.043 g, 46 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.38 – 7.20 (m, 40H), 6.64 (d, 4H, *J* = 2.4 Hz), 6.57 (d, 2H, *J* = 2.0 Hz), 6.53 (t, 2H, *J* = 2.4, 2.4 Hz), 6.47 (t, 1H, *J* = 2.0, 2.0 Hz), 4.98 (s, 8H), 4.90 (s, 4H), 4.51 (s, 2H), 4.48 – 4.45 (m, 12 H), 3.60 – 3.58 (m, 2H), 3.54 – 3.46 (m,12 H), 2.44 – 2.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 160.0, 144.4, 140.5, 139.3, 138.1, 136.8, 128.5, 128.3, 127.9, 127.60, 127.58, 127.5, 124.3, 106.7, 106.4, 101.6, 101.4, 78.5, 73.3, 72.2, 70.10, 70.05, 69.95, 68.1, 63.5, 48.3, 41.1 (Figure A.31, A.32).

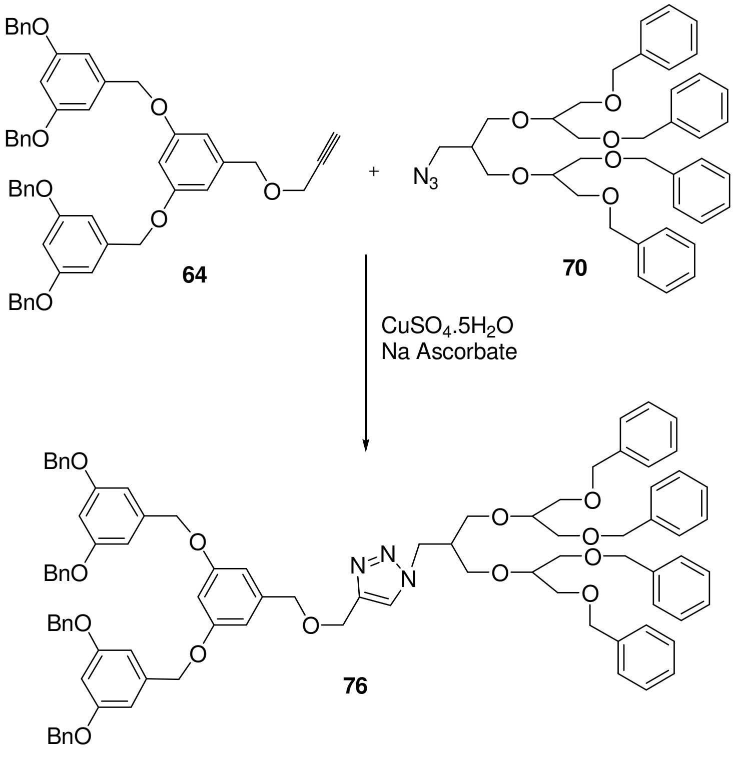


Figure 4.41. Coupling of A_2-acetylene with B_2-azide

4.5.6. Coupling of A_2-acetylene with B_2-azide-55°C

Prepared from A_2-acetylene **64** (0.049 g, 0.062 mmol) and B_2-azide **70** (0.042 g, 0.065 mmol) at 55°C according to the general procedure. The crude product was purified by column chromotography with ethyl acetate:hexane (1:1) as eluent to obtain A_2-B_2 **76** as a colorless oil (0.077 g, 88 % yield).

4.5.7. Coupling of B_2-acetylene with A_2-azide-room temperature

Prepared from B_2-acetylene **73** (0.033 g, 0.052 mmol) and A_2-azide **61** (0.041 g, 0.054 mmol) at room temperature according to the general procedure. The crude product was purified by column chromotography with ethyl acetate:hexane (1:1) as eluent to obtain B_2-A_2 **79** as a colorless oil (0.026 g, 22 % yield) ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 41H), 6.61 (bs, 4H), 6.54 – 6.50 (m, 3H), 6.40 (bs, 2H), 5.27 (s, 2H), 4.08 (s, 8H), 4.87 (s, 4H), 4.52 (s, 2H), 4.44 (s, 8H), 3.60 – 3.47 (m, 16H), 2.18 – 2.12 (m, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 160.2, 146.0, 138.9, 138.4, 136.9, 136.7, 128.5, 128.33, 128.27, 128.0, 127.52, 127.5, 122.3, 107.1, 106.4, 102.0, 101.7, 78.4, 73.4, 73.2, 70.1, 70.05, 70.00, 68.5, 64.8, 53.9, 40.8 (Figure A.33, A.34).

4.5.8. Coupling of B_2-acetylene with A_2-azide-55°C

Prepared from B_2-acetylene **73** (0.033 g, 0.052 mmol) and A_2-azide **61** (0.041 g, 0.054 mmol) at 55°C according to the general procedure. The crude product was purified by column chromotography with ethyl acetate:hexane (1:1) as eluent to obtain B_2-A_2 **79** as a colorless oil (0.06 g, 81 % yield).

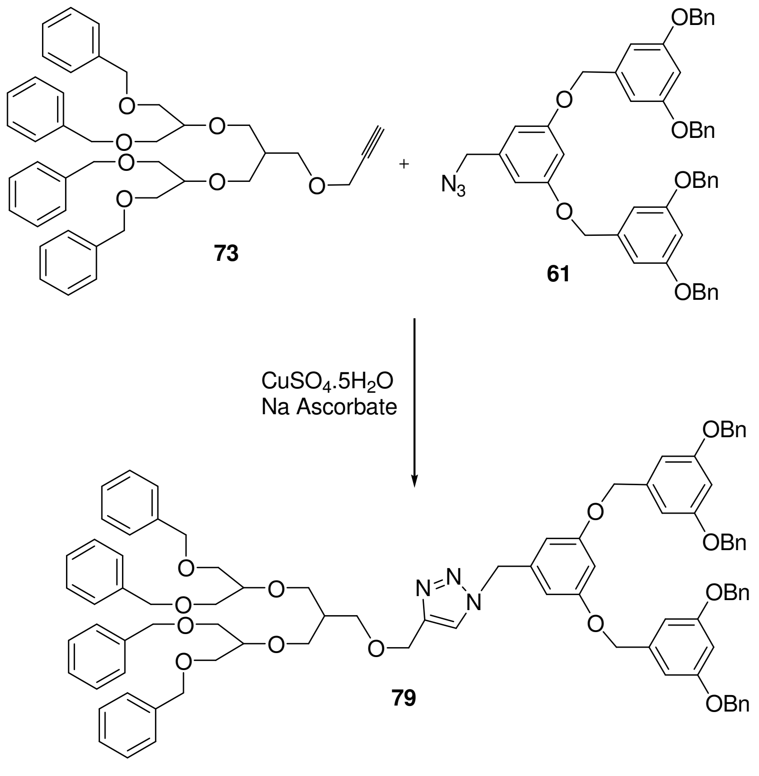


Figure 4.42. Coupling of B_2-acetylene with A_2-azide

4.5.9. Coupling of B_3-acetylene with A_3-azide-55°C

Prepared from B_3-acetylene **74** (60.0 mg, 0.044 mmol) and A_3-azide **62** (76.0 mg, 0.047 mmol) at 55°C according to the general procedure. The crude product was purified by column chromotography with ethyl acetate:hexane (1:1) as eluent to obtain A_3-B_3 **80** as a colorless oil (96.0 mg, 72 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 81H), 6.64 (d, 8H, J = 2.0 Hz), 6.60 (d, 4H, J = 2.0 Hz), 6.54 (t, 4H, J = 2.0 Hz), 6.51 (t, 3H, J = 2.0 Hz), 6.42 (d, 2H, J = 2.0 Hz), 5.26 (s, 2H), 4.97 (s, 16H), 4.91 (s, 8H), 4.85 (s, 4H), 4.48 (s, 2H), 4.44 (s, 16H), 3.59 – 3.46 (m, 38H), 2.13 – 2.08 (m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 160.1, 160.0, 139.2, 138.8, 138.4, 137.1, 136.7, 128.5, 128.2, 127.9, 127.49, 127.47, 127.42, 122.4, 107.1, 106.4, 101.9, 101.6, 78.3, 73.2, 70.1, 70.0, 69.5, 69.4, 69.2, 68.6, 64.7, 40.9, 40.2 (Figure A.35, A.36).

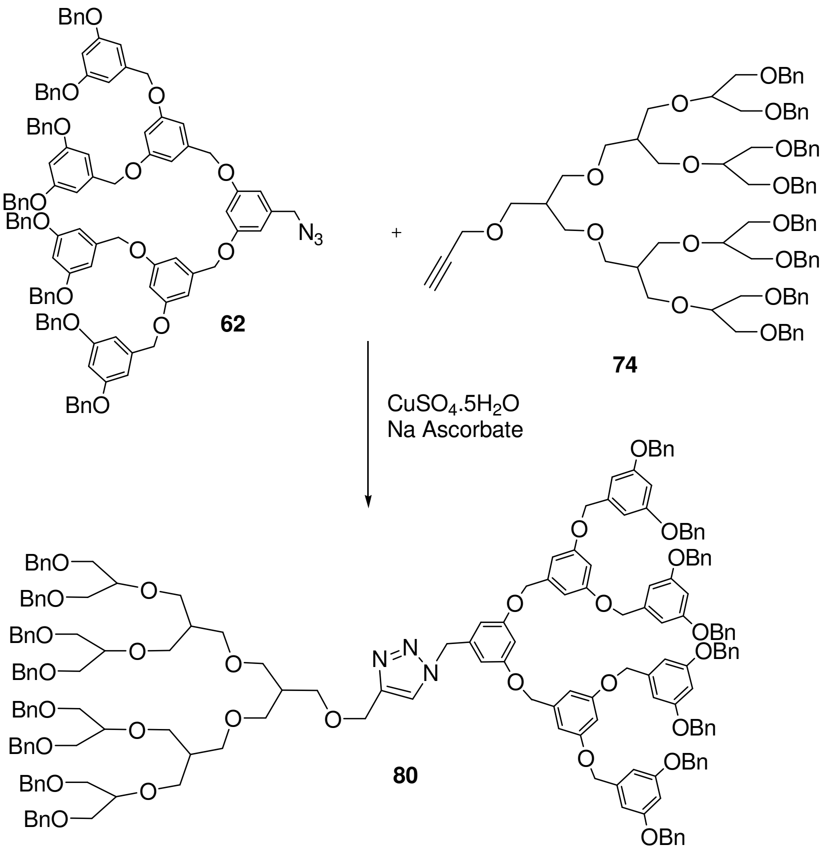


Figure 4.43. Coupling of B_3-acetylene with A_3-azide

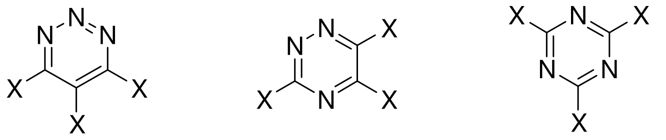
Table 4.1. Results of the click reactions

	RT	**55ºC**
A_1-B_1	80%	78%
B_1-A_1	50%	82%
A_2-B_2	46%	88%
B_2-A_2	22%	81%
B_3-A_3		72%

Poly (aryl ether) and polyether dendrons were synthesized to obtain a segment-block dendrimer via ‘click reaction’. For both of the dendrons convergent method is used and they were synthesized up to 3rd dendron. These dendrons were equipped with azide and alkyne functionality. For each generation of dendrons two sets of click reactions were performed: one set at room temperature and one set at 55°C (Table 4.1). It was seen that the reactions at 55°C had higher yields which means the reaction is thermodynamically driven and nonsymmetrical segment block dendrimers were obtained in excellent yields at higher temperatures

5. TRIAZINES AS BUILDING BLOCKS IN MACROMOLECULAR CHEMISTRY

The triazine structure is a heterocyclic ring, similar to a six membered benzene ring but instead, three carbons are replaced by nitrogen atoms. There are three different isomers which can be distinguished by the positions of the nitrogen atoms on the ring. These isomers are 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine (Figure 5.1). In the following sections the main properties of the 1,3,5-triazines will be discussed since they have been exploited in dendrimer synthesis.



1,2,3-Triazine 1,2,4-Triazine 1,3,5-Triazine

Figure 5.1. Isomeric structures of triazines

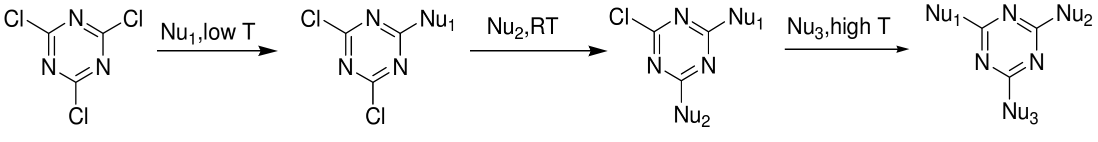
5.1. 1,3,5-Triazines

Since the early 1990s 1,3,5-triazine derivatives have been widely used as building blocks for supramolecules. The reason behind this fact is that triazine building blocks have synthetic diversity and the opportunities for molecular recognition. These two properties are very important in supramolecular chemistry because the need for synthesizing custom made materials involving molecular interactions is important.

5.1.1. 1,3,5-trichlorotriazine

One of the most widely used 1,3,5-triazines is 1,3,5-trichlorotriazine (**81**), commercially sold as cyanuric chloride. Cyanuric chloride was synthesized for the first time in 1827 and its precise composition was established by Liebig in 1829. It was synthesized by the cyclotrimerization of cyanogen chloride in the presence of activated charcoal as the catalyst [26].

The importance of this molecule comes from the fact that the degree of substitution can be controlled by the applied temperature. While the first substitution is generally very vigorous (even at temperatures below 0ºC), the second and the third substitutions will obviously require higher temperatures due to the fact that an electron donating species is introduced into the system and thus the electron density on the system increases (Figure 5.2). On behalf of this information, we propose that one can prepare segment block dendrimers with cyanuric chloride via using the chemical reactivity difference at different temperatures.



81 **82** **83** **84**

Figure 5.2. Chemoselective reactivity of cyanuric chloride

Usage of cyanuric chloride as a core molecule also brings the advantage of growing dendrons with lower number of reactions per generation compared to the traditional convergent synthesis methods. The best example can be the comparison of cyanuric chloride with Fréchet's 3,5-dihydroxybenzyl alcohol core (Figure 5.3). Fréchet's monomer contains three nucleophilic sites. The phenol groups are more nucleophilic then the benzylic alcohol so they react first with the nucleophiles. Then, to grow the dendron to the next generation, the alcohol functionality on the core is converted into an electrophile. Whereas, in a triazine core there are already three electrophiles. Each of these electrophilic groups can be substituted by a nucleophile in one step without any functional group interconversion and thus reducing the number of steps to reach the same generation.

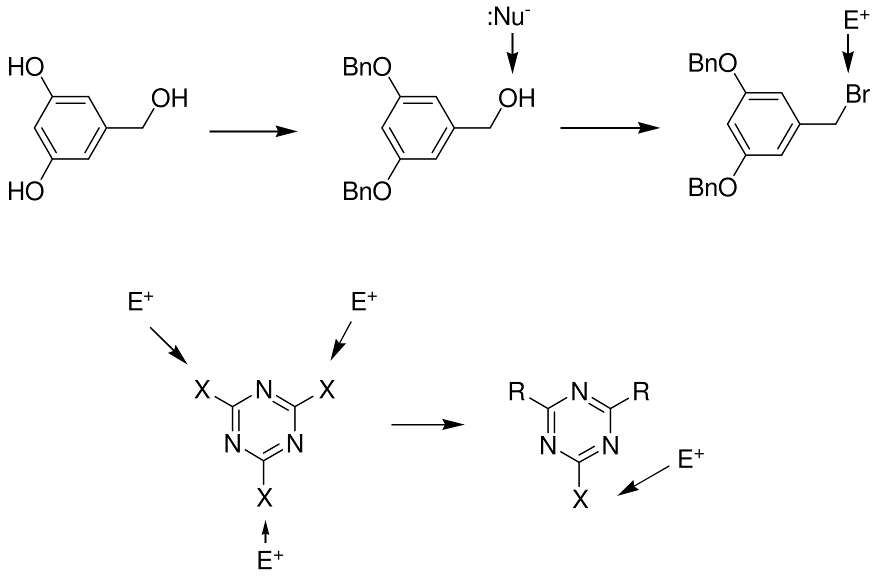


Figure 5.3. Fréchet's monomer versus triazines

As a result, it's advantageous to use triazines for dendrimer synthesis and there are many examples in the literature indicating the importance of triazines in macromolecular synthesis. Although the triazine units have been used as building blocks in dendrimer synthesis, there is no report regarding potential usage as a trifunctional core unit.

5.2. Triazine Dendrimers

Today, there are three main methods that have been reported to synthesize triazine based dendrimers. The first utilizes cycloaddition reactions to form the triazine ring. The second route uses cyanuric chloride, which has different chemoselectivity at different temperatures. The third method involves the preparation of hyperbranched molecules and then using them for synthesizing the dendritic structures. Each of these will be discussed in detail in the following sections.

5.2.1. Cycloaddition Method

Cycloaddition method is simply the reaction of a nitrile of choice with a guanidine derivative which has a nitrile substitution on it (Figure 5.4). The reaction requires the presence of a base, such as potassium or sodium hydroxide, at elevated temperatures.

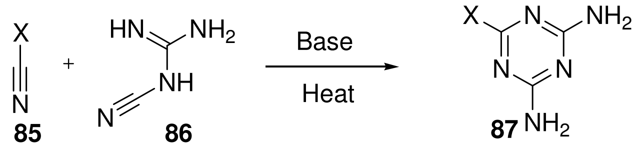


Figure 5.4. An example for cycloaddition method

The first example of a triazine based dendrimer, which was synthesized divergently by the cycloaddition method, was done by Maciejewski and coworkers in 1994 [27]. They prepared an amine terminated dendrimer by the cycloaddition reaction between a guanidine derivative having a nitrile substitution on it and a terminal nitrile as described above (Figure 5.5).

The strategy is simple: by the cyanoethylation of a pendant amine we obtain a dendron which has twice the number of the nitrile groups. Then, the dendrimer generation was increased by the cycloaddition reaction between the peripheral nitriles and nitrile substituted guanidine derivatives.

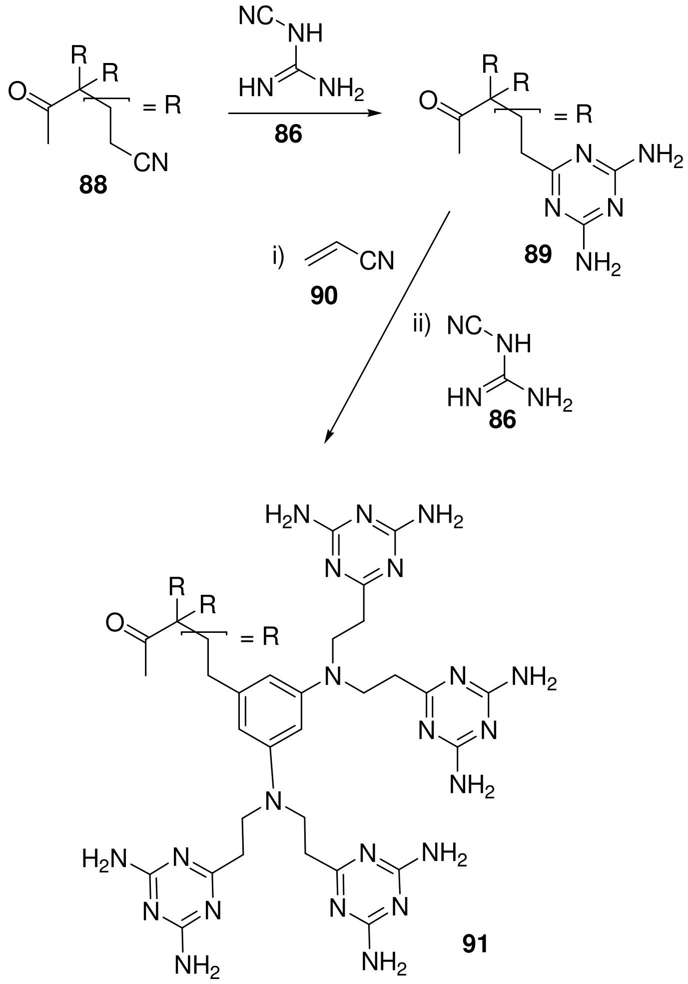
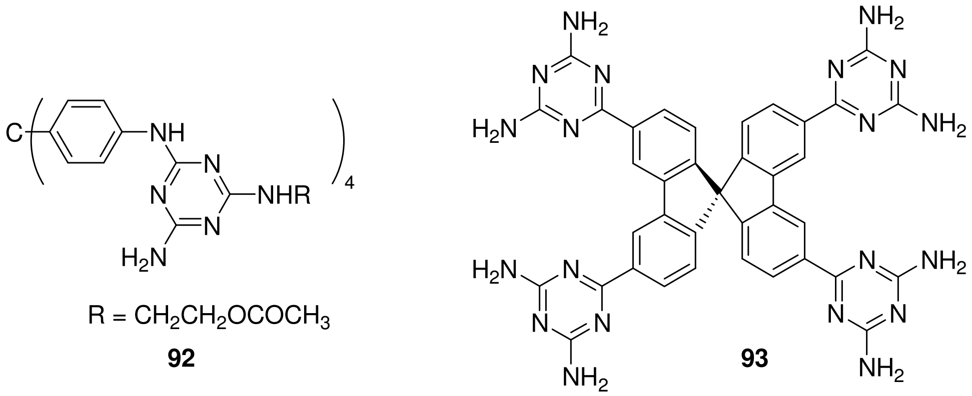


Figure 5.5. The first triazine based dendrimer synthesized by cycloaddition method

Another example where the cycloaddition method was used to build triazine-based dendrimers is done by Wuest and coworkers [28]. They synthesized triazine-based dendrimers which can be used as tectons in solid state networks that has controlled porosity (Figure 5.6). Tectons are molecules which have dominant specific attractive forces that causes the assembly of the aggregates to have controllable geometries. In this work, they prepared the tectons using the precursor nitrile and dicyandiamide in 90 % yield.



R = $CH_2CH_2OCOCH_3$

92

93

Figure 5.6. Examples of tectons that are used for solid state networks

5.2.2. Nucleophilic Aromatic Substitution Method

Majority of triazine based dendrimers are synthesized by nucleophilic aromatic substitution on cyanuric chloride. The synthesis is relatively easy because of the chemoselectivity of cyanuric chloride at different temperatures as explained before.

One of the first examples was reported in 1996, where the reaction of m-bis(methylamino)benzene with 2 equivalents of cyanuric chloride yield in a dendritic product that incorporated triazine groups (Figure 5.7). This particular dendron was tested as chelating ligand for Gd in magnetic resonance imaging applications [29].

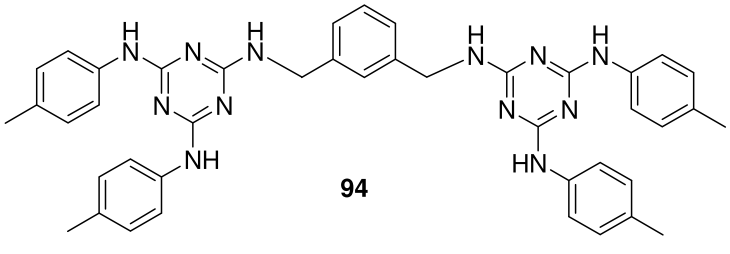


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Figure 5.7. A dendritic molecule that is used for magnetic resonance applications

In 2000, Simanek and coworkers synthesized a third generation dendrimer by using convergent and divergent method (Figure 5.8) [30]. The dendrimer was based on melamines which are one of the most widely used triazines. Melamines also have the ability to recognize other molecules by making hydrogen bonds, π-π interactions and metal chelation so they are important for many applications. In this work, they used diamine linkers and cyanuric chloride to construct the dendrimer. The overall yield they got from the divergent synthesis was 1 % whereas the convergent route provided higher yields. So they achieved the synthesis of a triazine based dendrimer by nucleophilic substitution, under moderate reaction conditions for the first time.

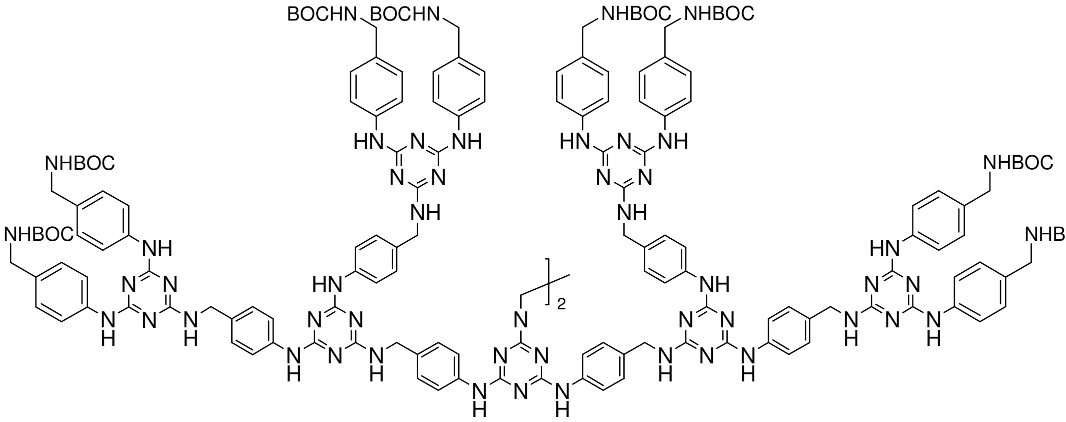

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Figure 5.8. A third generation melamine-based dendrimer

In another study, Namazi and Adeli synthesized a triazine based dendritic block copolymer that has a polyethylene glycol (PEG) unit as the core (Figure 5.9) [31]. First, they reacted PEG with cyanuric chloride and then, by sequential treatment of this product with ethanolamine, followed by cyanuric chloride they increased the generations of the dendrimer. Since the resulting dendritic block copolymers were amphiphilic, they also investigated the micellar properties of these compounds with using fluorescence spectroscopy.

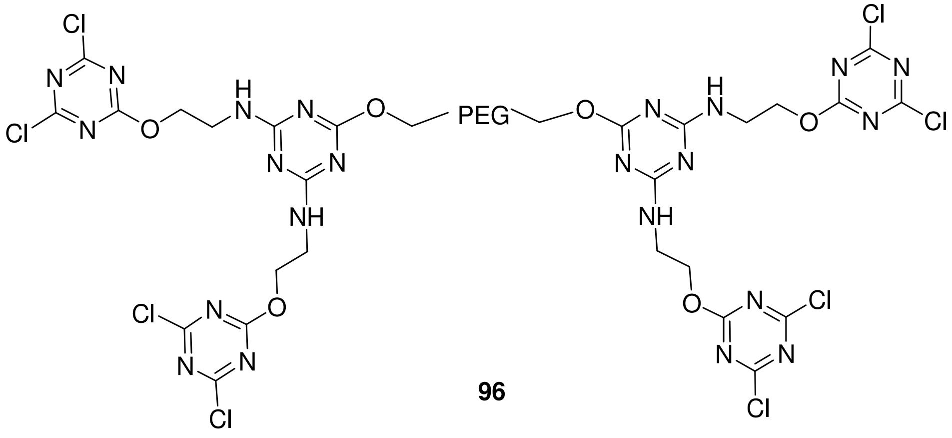

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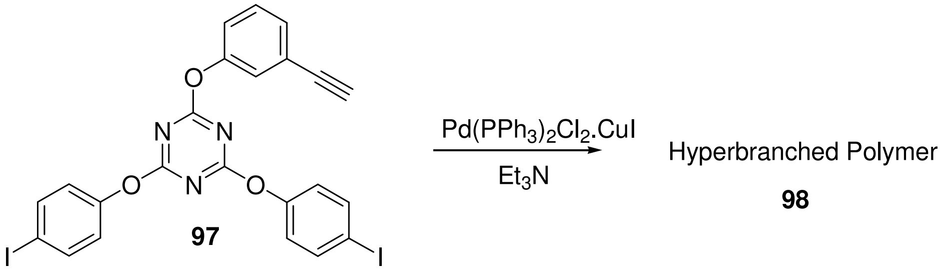
Figure 5.9. Triazine based dendritic block copolymer

5.2.3. Hyperbranched Molecules

The last method that is used for the synthesis of triazine based dendrimers goes through the synthesis of hyperbranched monomers. By using these monomers the synthesis of hyperbranched polymers is possible.

One of the examples for the usage of hyperbranched molecules was reported by Kim and coworkers [32]. They used the Heck coupling reaction to prepare hyperbranched triazine polymers from AB_2 type triazine monomer (Figure 5.10). They were able to synthesize hyperbranched polymers which have molecular weights ranging between 6000 – 10000 g mol $^{-1}$. The advantage of this procedure is that one can prepare high molecular weight materials by using single-pot procedures.



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98

Figure 5.10. Heck coupling of an AB_2 monomer to yield in hyperbranched polymer

In another study, Kim and coworkers synthesized two different types of triazine monomers (Figure 5.11) and heated them in the presence of potassium carbonate to 140ºC [33]. As a result they obtained polymers which had molecular weight values ranging from 11000 to 15000 g mol $^{-1}$ and showed an excellent thermal stability.

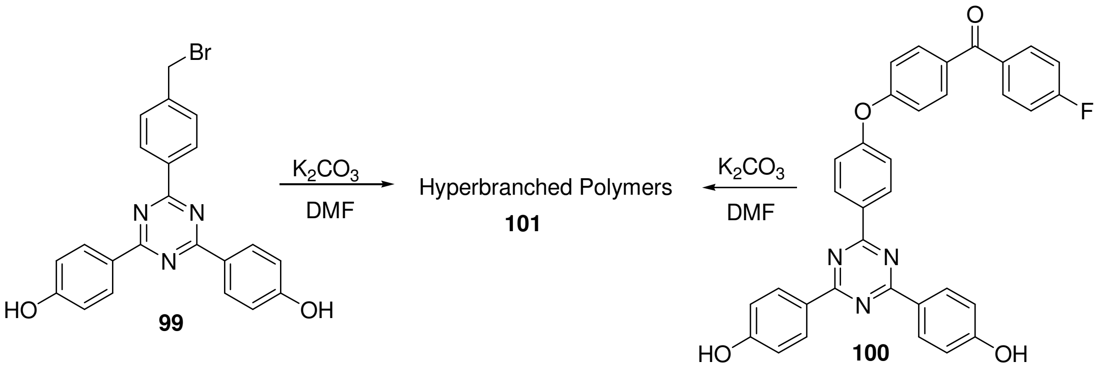


Figure 5.11. A different route to hyperbranched polymers

5.3. Application Areas of Triazine Dendrimers

Triazine dendrimers has potential usage in different application areas such as molecular recognition, supramolecular self assembly, decoration of inorganic supports, surfactants, medicinal chemistry applications, energy-harvesting and emitting applications, etc. A few examples are discussed below to highlight potential applications.

Melamine based triazine structures have the ability for molecular recognition. An example based on this property was reported by Fréchet and coworkers in which they attached two complementary hydrogen bonding groups into the focal point of different dendrons [34]. They used melamine and cyanuric acid derivatives for this purpose and investigated the supramolecular self assembly of higher generation dendrimers. Melamine and cyanuric acid derivatives were attached to dendrons of generations 2 and 4 and it was seen that second generation dendrons formed the expected self assembly (Figure 5.12) whereas higher generations of dendrons formed aggregates of different kinds.

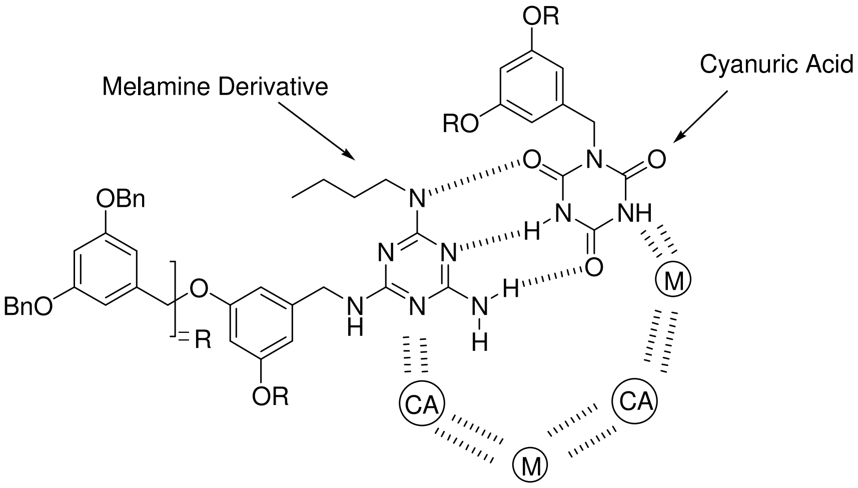
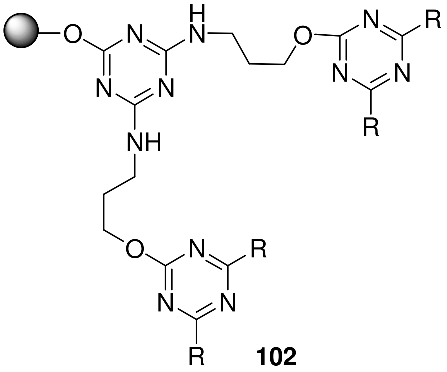


Figure 5.12. Supramolecular self-assembly formation

Melamine based dendrimers can also be used as proton scavengers. The use of scavenger resins is of importance for purification of the reaction products. The problem with these resins is that large amounts should be used in order to get rid of all the side products and this can cause physical difficulties especially in small scale reactions. In order to get rid of this problem high loading resins should be synthesized so that we can obtain the same efficiency with small amounts of the resin. This can be done via using dendritic resins which are bounded on solid supports. Melamines attached onto an alcohol functionalized Wang resin can be used as high loading resins and efficient proton scavengers. Examples of such resins are reported by Smith et al. [35] in 2000 (Figure 5.13).



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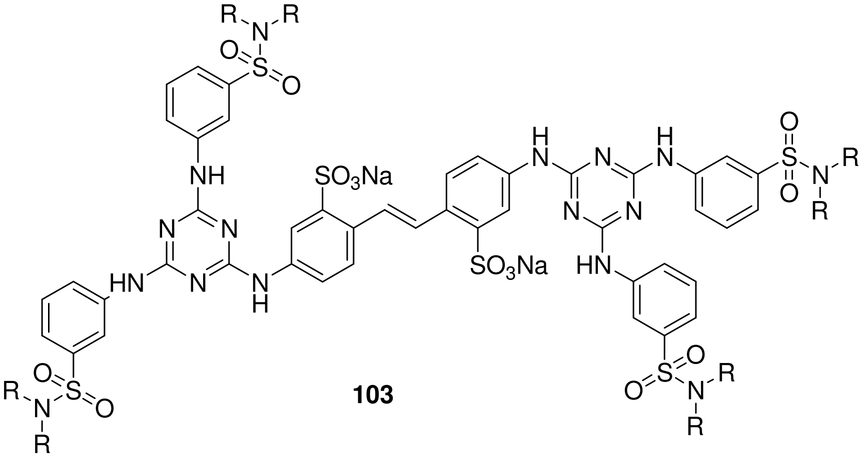
R=$NHCH_2CH_2CH_2OH$

Figure 5.13. Proton scavenger resin based on triazine dendrimers

Dendrimers that contain multiple triazine groups can have activity as antiviral agents. In 1992 a program was started by a company in order to find compounds that inhibit the activity of the human respiratory syncytial virus (RSV). The active compound CL 309623 was found to be a dendritic structure which has a disulfonated stilbene core with a triazine unit at each end of the core (Figure 5.14) [36].



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R=$CH_2CH_2CONH_2$

Figure 5.14. Structure of a dendritic antiviral agent (CL 309623)

As can be seen from the literature examples, the use of triazines as building blocks for dendrons and dendrimers is quite popular. The methods of synthesis are straightforward and the yields are quite high so it is advantageous to synthesize triazine-based molecules.

6. RESULTS AND DISCUSSION – PART B

6.1. Aim of the Study

As explained in the first chapter, dendrimers are highly branched, well defined, globular macromolecules which have been anticipated to be used as drug delivery vehicles because of the different functional groups they have at their periphery. Once the drug is attached onto a dendrimer the remaining functional groups can be used for improving the solubility of the drug and for targeted drug delivery purposes. One can see the need for the efficient synthesis of dendrimers with different functionalities at their periphery.

Triazines can be used for the divergent and convergent synthesis of dendrimers. The main advantage is we don't need to functionalize the core to generate the dendrimer growth because the core already has three electrophilic sites which can be substituted by different kinds of nucleophilic groups via nucleophilic substitution reaction.

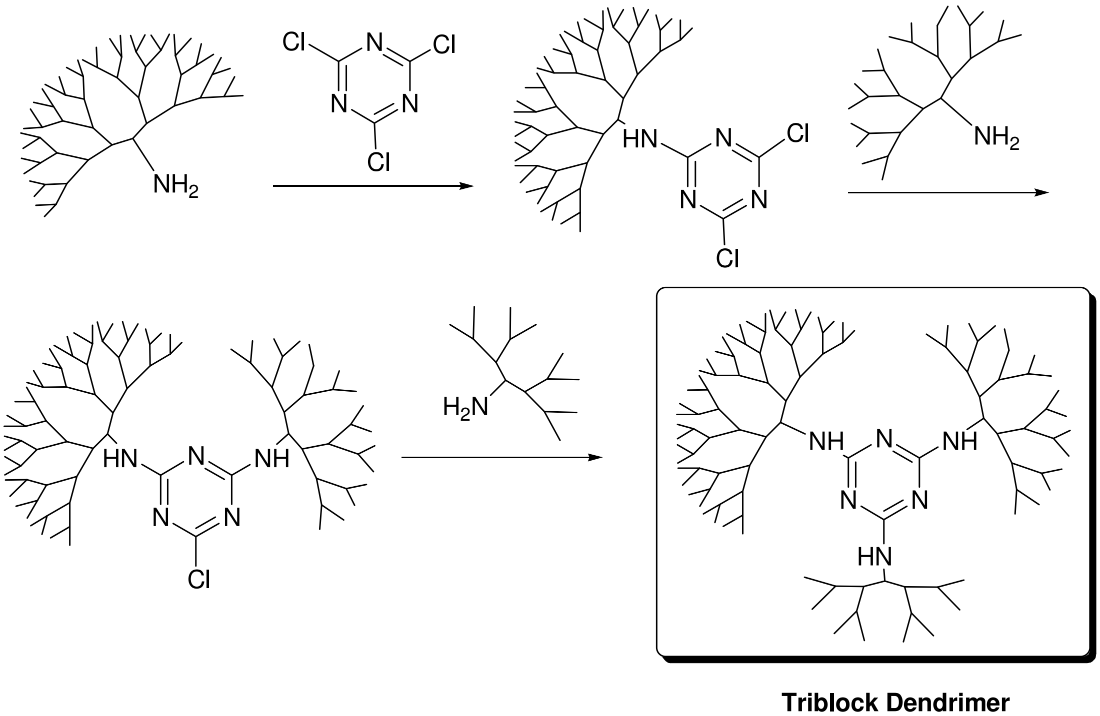


Figure 6.1. A triblock dendrimer using a triazine core

To the best of our knowledge there is no example of a nonsymmetrical macromolecule which has different dendritic structures as substituents that has been attached into a single cyanuric chloride unit. In this study, we evaluated attachment of different kinds of dendritic structures to a 1,3,5- trichlorotriazine based core by using the sequential reactions.

For this purpose, we used simpler molecules to see the effect of substitution on the triazine core. We started with monosubstitution of the triazine core with Fréchet's first generation alcohol and grow the molecule by the sequential reactions with benzylamine and octylamine. The experimental results are given in the following sections.

6.2. Synthesis of Dendrons

Fréchet's first generation poly (aryl ether) dendron was synthesized according to the procedures in the 4th chapter adopted from a report by Fréchet and Hawker [8].

6.2.1. Synthesis of G_1-amine

To a stirring solution of G_1-azide **60** (3 g, 8.84 mmol) in dry THF (141 mL), $LiAlH_4$ (1.34 g, 35.36 mmol) was added very slowly at 0ºC under N_2. The reaction mixture was refluxed at 65°C under N_2 for 4 h with the progress of the reaction being monitored by TLC. After all of the G_1-azide **60** had reacted, water (10 mL) was added slowly to decompose the excess $LiAlH_4$. Then, the reaction mixture was extracted with EtOAc (3 x 25 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. The volatiles were removed under *vacuo*. The crude product was purified by column chromatography eluting with CH_2Cl_2 first and then with methanol:CH_2Cl_2 (1:9) to give G_1-amine **104** as a yellow oil (2.71 g, 96 % yield) ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 10H), 6.57 (d, 2H, *J* = 2.0 Hz), 6.50 (t, 1H, *J* = 2.0 Hz), 5.02 (s, 4H), 3.80 (s, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 145.7, 136.9, 128.5, 127.9, 127.4, 106.1, 100.5, 70.0, 46.5 (Figure A.37, 38).

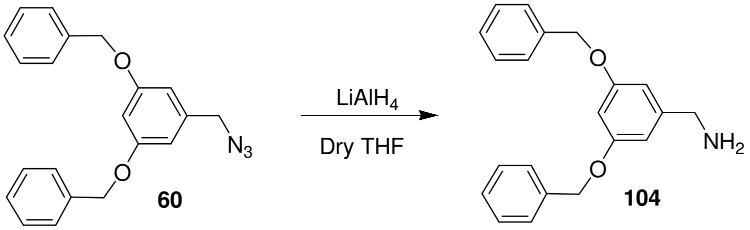


Figure 6.2. Synthesis of G_1-amine

6.3. Synthesis of Triazine Compounds

6.3.1. Synthesis of G_1-alcohol substituted cyanuric chloride

To a stirring solution of cyanuric chloride **81** (1.72 g, 9.37 mmol) and N,N-diisopropylethylamine (2.13 mL, 12.5 mmol) in dry THF (25 mL) was added G_1-alcohol **43** (1.00 g, 3.12 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 h with the progress of the reaction being monitored by TLC. After all of the G_1-alcohol **43** was reacted the reaction mixture was filtered and the volatiles were removed under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (1:9) as eluent to obtain pure product **105** as a white powder (1.22 g, 83 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.42 - 7.30 (m, 10H), 6.68 (bs, 2H), 6.62 (bs, 1H), 5.43 (s, 2H), 5.03 (s, 4H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 170.8, 160.1, 136.5, 135.9, 128.5, 128.0, 127.4, 107.3, 102.6, 71.3, 70.1 (Figure A.39, 40).

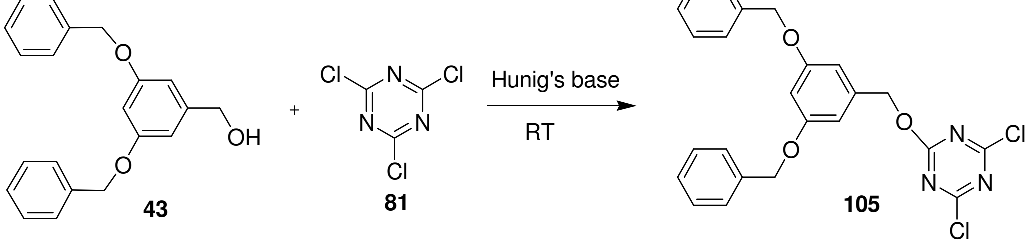


Figure 6.3. Synthesis of G_1-alcohol substituted cyanuric chloride

6.3.2. Synthesis of G_1-amine substituted cyanuric chloride

To a stirring solution of G_1-amine **104** (0.159 g, 0.5 mmol) and N,N-diisopropylethylamine (0.26 mL, 1.52 mmol) in dry THF (5 mL) at -10°C was added cyanuric chloride **81** (0.092 g, 0.50 mmol). The reaction mixture was stirred at -10ºC for 3 h with the progress of the reaction being monitored by TLC. After all of the G_1-amine **104** was reacted, the reaction mixture was filtered and the volatiles were removed under *vacuo*. The residue was partitioned between CH_2Cl_2 and brine and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (1:3) as eluent to obtain the product **106** as a white powder (0.177 g, 76 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.39 - 7.29 (m, 10H), 6.55 (t, 1H, *J* = 2.4 Hz), 6.49 (d, 2H, *J* = 2.4 Hz), 6.06 (bs, 1H), 5.01 (s, 4H), 4.57 (d, 2H, *J* = 3.6 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.1, 165.8, 160.3, 138.5, 136.5, 128.6, 128.1, 127.4, 106.7, 101.5, 70.2, 45.4 (Figure A.41, A.42).

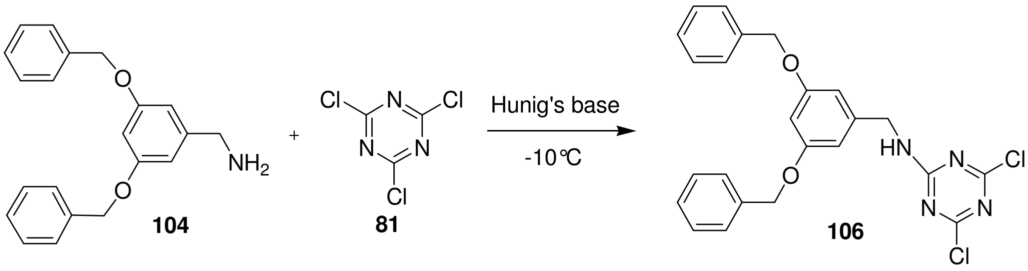


Figure 6.4. Synthesis of G_1-amine substituted cyanuric chloride

6.3.3. Synthesis of octylamine substituted cyanuric chloride

To a stirring solution of octylamine **107** (0.16 mL, 1.00 mmol) and N,N-diisopropylethylamine (0.51 mL, 3.00 mmol) in dry THF (5 mL) at -10°C was added cyanuric chloride **81** (0.20 g, 1.10 mmol). The reaction mixture was stirred at -10ºC for 3 h with the progress of the reaction being monitored by TLC. After all of the octylamine **107** was reacted the reaction mixture was filtered and the volatiles were removed under *vacuo*. The residue was partitioned between CH_2Cl_2 and brine and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (1:19) as eluent to obtain the pure product **108** as a white powder (0.269 g, 97 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.81 (bs, 1H), 3.45 (m, 2H), 1.58 (tt, 2H, *J* = 7.2, 7.2 Hz), 1.35 – 1.26 (m, 10H), 0.87 (t, 3H, *J* = 6.8 Hz) corresponding to the literature values [37] (Figure A.43).

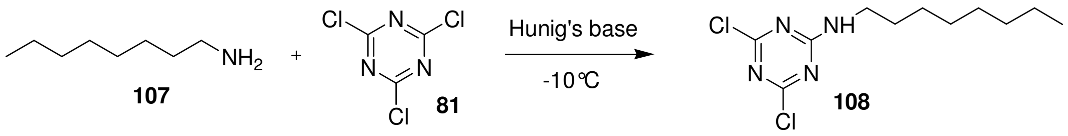


Figure 6.5. Synthesis of octylamine substituted cyanuric chloride

6.3.4. Synthesis of benzylamine substituted cyanuric chloride

To a stirring solution of benzylamine **109** (0.109 mL, 1.00 mmol) and N,N-diisopropylethylamine (0.51 mL, 3.00 mmol) in dry THF (5 mL) at -10°C was added cyanuric chloride **81** (0.202 g, 1.10 mmol). The reaction mixture was stirred at -10ºC for 3 h with the progress of the reaction being monitored by TLC. After all of the benzylamine **109** was reacted the reaction mixture was filtered and the volatiles were removed under *vacuo*. The residue was partitioned between CH_2Cl_2 and brine and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (2:23) as eluent to obtain the pure product **110** as a white powder (0.154 g, 60 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.37 - 7.27 (m, 5H), 6.31 (bs, 1H), 4.66 (d, 2H, *J* = 6.4 Hz) corresponding to the literature values [38] (Figure A.44).

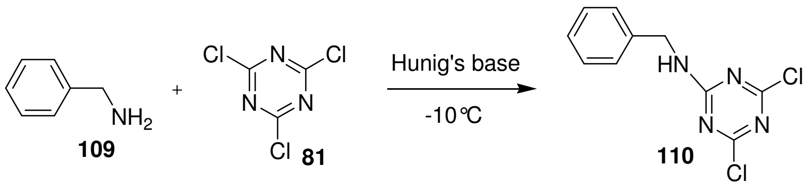


Figure 6.6. Synthesis of benzylamine substituted cyanuric chloride

6.3.5. Synthesis of Disubstituted Triazine (G_1-alcohol and octylamine)

To a stirring solution of G_1-alcohol substituted cyanuric chloride **105** (0.25 g, 0.53 mmol) and N,N-diisopropylethylamine (0.27 mL, 1.60 mmol) in dry THF (6.0 mL) at room temperature was added octylamine **107** (1 mL, 1.10 mmol) and methanol (1.0 mL). The reaction mixture was stirred at room temperature for 24 h with the progress of the reaction being monitored by TLC. After all of the starting material **105** was reacted the reaction mixture was filtered and the volatiles were removed under *vacuo*. The residue was partitioned between CH_2Cl_2 and brine and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (3:17) as eluent to obtain the pure product **111** as a white powder (0.142 g, 48 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 10H), 6.67 (d, 1.33H, J = 2.4 Hz), 6.64 (d, 0.66 H, J = 2.4 Hz), 6.56 (t, 1H, J = 2.4 Hz), 5.33 (s, 1.33H), 5.30 (s, 0.66H), 5.01 (s, 4H), 3.46 – 3.37 (m, 2H), 1.58 – 1.50 (m, 2H), 1.26 – 1.24 (m, 10H), 0.85 (t, 3H, J = 6.8 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.5, 170.0, 169.9, 166.8, 160.0, 137.7, 136.6, 128.4, 127.8, 127.3, 106.9, 101.9, 70.0, 69.4, 41.2, 31.7, 29.1, 26.7, 22.5, 14.0 (Figure A.45, A.46).

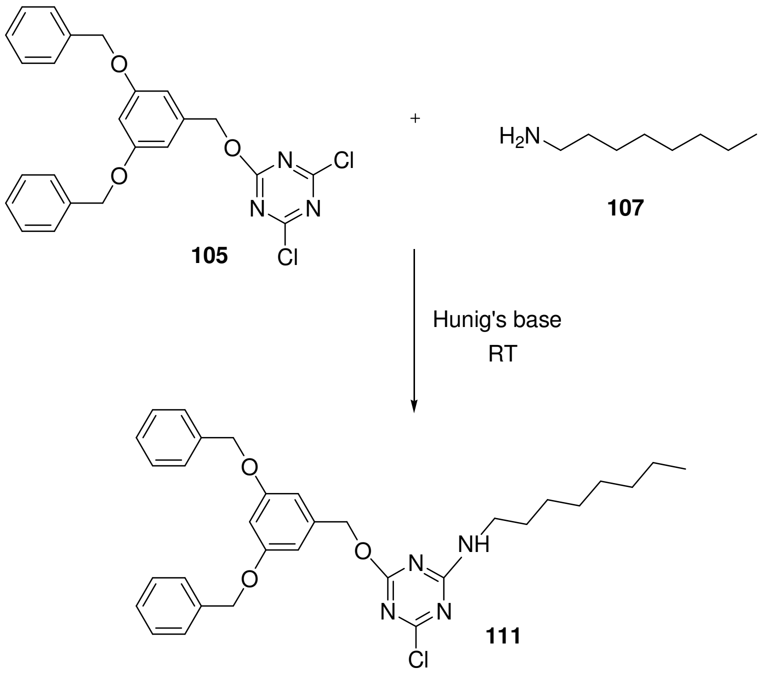


Figure 6.7. Synthesis of disubstituted triazine **111**

6.3.6. Synthesis of Disubstituted Triazine (G_1-alcohol and benzylamine)

To a stirring solution of G_1-alcohol substituted cyanuric chloride **105** (0.21 g, 0.49 mmol) and N,N-diisopropylethylamine (0.22 mL, 1.48 mmol) in dry THF (5.0 mL) at room temperature was added benzylamine **109** (0.054 mL, 1.10 mmol) and methanol (1.0 mL). The reaction mixture was stirred at room temperature for 24 h with the progress of the reaction being monitored by TLC. After all of the starting material **105** was reacted the reaction mixture was filtered and the volatiles were removed under *vacuo*. The residue was partitioned between CH_2Cl_2 and brine and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (1:9) as eluent to obtain the pure product **112** as a white powder (0.125 g, 47 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 15H), 6.65 – 6.63 (m, 2H), 6.57 – 6.56 (m, 1H), 6.20 (bs, 1H), 5.32 (s, 2H), 5.00 (s, 4H), 4.65 (d, *J* = 6.0, 0.66H), 4.61 (d, *J* 6.4, 1.33H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.6, 170.5, 170.1, 167.0, 166.9, 160.03, 160.01, 137.64, 137.55, 137.23, 137.20, 136.7, 128.8, 128.7, 128.6, 128.0, 127.8, 127.7, 127.5, 107.0, 106.9, 102.1, 70.1, 69.6, 69.4, 45.2, 45.0 (Figure A.47, A.48).

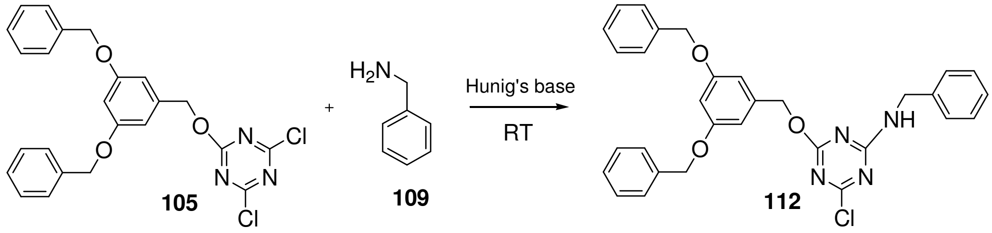


Figure 6.8. Synthesis of disubstituted triazine **112**

6.3.7. Synthesis of Disubstituted Triazine (G_1-alcohol and G_1-amine)

To a stirring solution of G_1-alcohol substituted cyanuric chloride **105** (0.25 g, 0.53 mmol) and N,N-diisopropyl ethylamine (0.27 mL, 1.60 mmol) in dry THF (5.0 mL) at room temperature was added G_1-amine **104** (0.18 g, 0.58 mmol) and methanol (1.0 mL). The reaction mixture was stirred at room temperature for 24 h with the progress of the reaction being monitored by TLC. After all of the starting material **105** was reacted the reaction mixture was filtered and the volatiles were removed under *vacuo*. The residue was partitioned between CH_2Cl_2 and brine and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and then the solvent was evaporated under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (1:3) as eluent to obtain the pure product **113** as a white powder (0.21 g, 55 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.46 – 7.32 (m, 20H), 6.73 (d, 1.33H, J = 2.4 Hz), 6.70 (d, 0.66H, J = 2.4 Hz), 6.45 – 6.60 (m, 2H), 6.58 (bs, 2H), 5.32 (s, 1.33H), 5.31 (s, 0.66H), 5.03 (s, 1.33H), 5.02 (s, 2.66H), 5.00 (s, 1.33H), 4.99 (s, 2.66H), 4.62 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.3, 170.0, 169.8, 166.8, 166.7, 159.9, 159.8, 139.9, 139.8, 137.5, 137.3, 136.5, 128.4, 127.8, 127.3, 127.2, 106.8, 106.7, 106.4, 106.1, 101.9, 101.8, 100.9, 100.8, 69.80, 69.78, 69.4, 69.3, 44.71, 44.66 (Figure A.49, A.50).

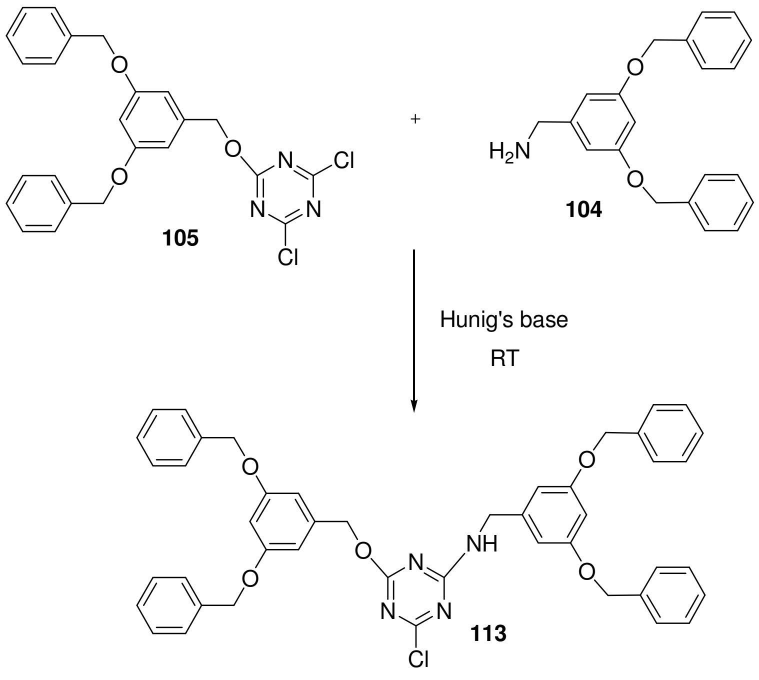


Figure 6.9. Synthesis of disubstituted triazine **113**

For unambiguous determination of structure of trisubstituted triazine, the same compound was synthesized using two different routes.

6.3.8. Synthesis of Trisubstituted Triazine 114 Route A

To a stirring solution of disubstituted triazine **111** (0.13 g, 0.23 mmol) in THF (2.0 mL) at room temperature was added benzylamine **109** (0.05 mL, 0.46 mmol) and N,N-diisopropylethylamine (0.067 mL, 0.38 mmol). The reaction mixture was stirred at room temperature for 24 h and then, for another 24 h refluxing at 85°C with the progress of the reaction being monitored by TLC. After all of the starting material **111** was reacted the reaction mixture was filtered and the volatiles were removed under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (2:3) as eluent to obtain the pure product **114** as a colorless oil (0.10 g, 70 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 15H), 6.68 (bs, 2H), 6.54 (dd, 1H, *J* = 2.0, 2.0Hz), 5.82 (bs, 0.33H), 5.62 (bs, 0.66H), 5.28 – 5.15 (m, 2H), 5.00 (s, 4H), 4.59 (bs, 2H), 3.35 (bs, 2H), 1.53 – 1.50 (m,2H), 1.27 – 1.25 (m,10H), 0.87 (t, 3H, *J* = 6.4Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.0, 167.2, 166.8, 159.9, 139.2, 139.8, 136.8, 128.5, 127.9, 127.4, 127.2, 107.0, 106.7, 101.6, 70.0, 68.0, 67.7, 44.8, 44.6, 40.9, 31.8, 29.6, 29.3, 29.2, 26.9, 22.6, 14.0 (Figure A.51, A.52).

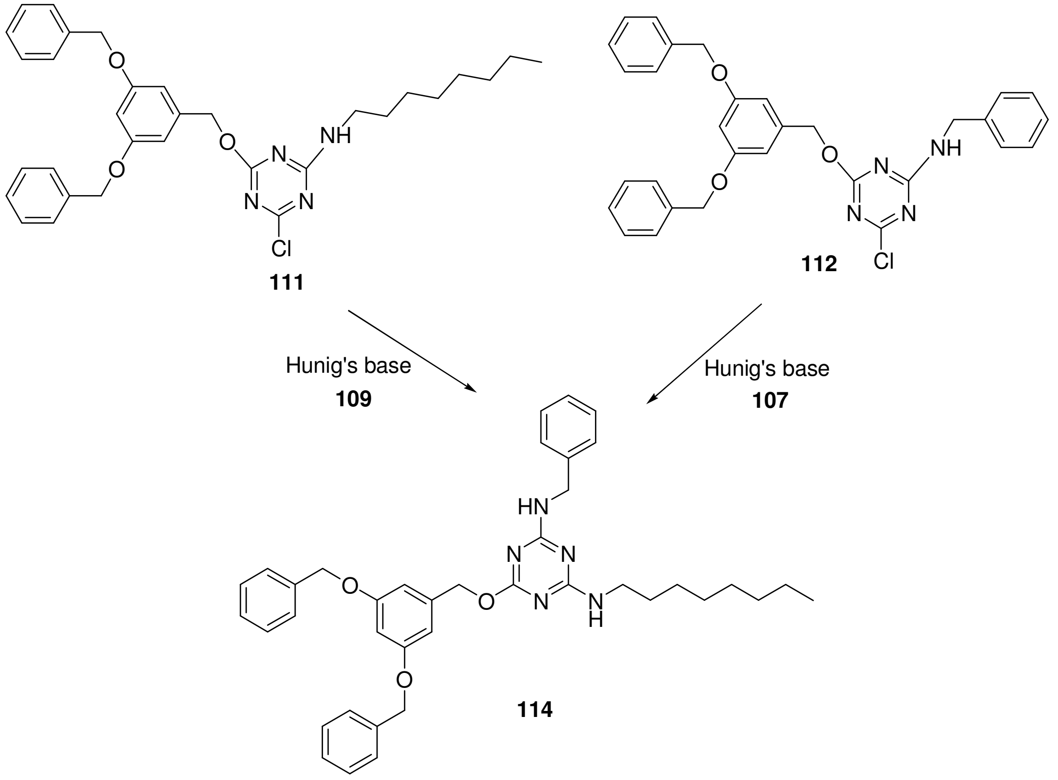


Figure 6.10. Synthesis of trisubstituted triazine **114**

6.3.9. Synthesis of Trisubstituted Triazine 114 Route B

To a stirring solution of disubstituted triazine **112** (G_1-alcohol and benzylamine) (0.6 g, 0.11 mmol) in THF (2.0 mL) at room temperature was added octylamine **107** (0.036 mL, 0.22 mmol) and N,N-diisopropylethylamine (0.032 mL, 0.18 mmol). The reaction mixture was stirred at room temperature for 24 h and then, for another 24 h refluxing at 85°C with the progress of the reaction being monitored by TLC. After all of the starting material **112** was reacted the reaction mixture was filtered and the volatiles were removed under *vacuo*. The crude product was purified by column chromotography with ethyl acetate:hexane (2:3) as eluent to obtain the pure product **114** as a colorless oil (0.05 g, 72 % yield). ^{1}HNMR (400 MHz, CDCl3) δ 7.41 – 7.23 (m, 15H), 6.69 (bs, 2H), 6.55 (bs, 1H), 5.98 (bs, 0.33H), 5.76 (bs, 0.66H), 5.29 – 5.18 (m, 2H), 5.00 (s, 4H), 4.60 (bs, 2H), 3.35 (bs, 2H), 1.52 –

1.50 (m, 2H), 1.28 – 1.26 (m, 10H), 0.88 (t, 3H, *J* = 6.4 Hz) ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.6, 170.0, 167.3, 166.9, 159.9, 139.2, 138.9, 136.8, 128.4, 127.8, 127.4, 127.1, 106.9, 106.7, 101.6, 70.0, 67.9, 67.7, 44.7, 44.6, 40.8, 31.8, 29.6, 29.24, 29.17, 26.8, 22.6, 14.0 (Figure A.53, A.54) data matching with the compound synthesized through Route A.

The experimental data that we have obtained from our experiments shows that trisubstitution on the cyanuric chloride core was successful. Further studies will be done towards the substitution of different dendritic structures on a cyanuric chloride core to obtain segmented triblock dendrimers.

7. CONCLUSIONS

Poly (aryl ether) and polyether dendrons were synthesized to obtain a segment-block dendrimer via ‘click reaction’. For both of the dendrons convergent method is used and they were synthesized up to 3rd dendron. These dendrons were equipped with azide and alkyne functionality. For each generation of dendrons two sets of click reactions were performed: one set at room temperature and one set at 55°C. It was seen that the reactions at 55°C had higher yields which means the reaction is thermodynamically driven and nonsymmetrical segment block dendrimers were obtained in excellent yields at higher temperatures.

In the second part, the preliminary studies to attach different kinds of dendritic structures to a 1,3,5-trichlorotriazine (cyanuric chloride) based core was done. For that the chemoselective reactivity difference of cyanuric chloride at different temperatures was taken into account. The sequential reactions leading to mono, di and trisubstituted cyanuric chloride were achieved by using Fréchet’s first generation alcohol, the corresponding first generation amine, benzylamine and octylamine as the model compounds. As a result, it was seen that the trisubstitution on the cyanuric chloride core was successful. Further studies will be done towards the substitution of different dendritic structures on a cyanuric chloride core to obtain segmented triblock dendrimers.

APPENDIX A: SPECTROSCOPY DATA

1H and 13C NMR spectroscopy data for the synthesized compounds are given. Needed regions of NMR data were expanded.

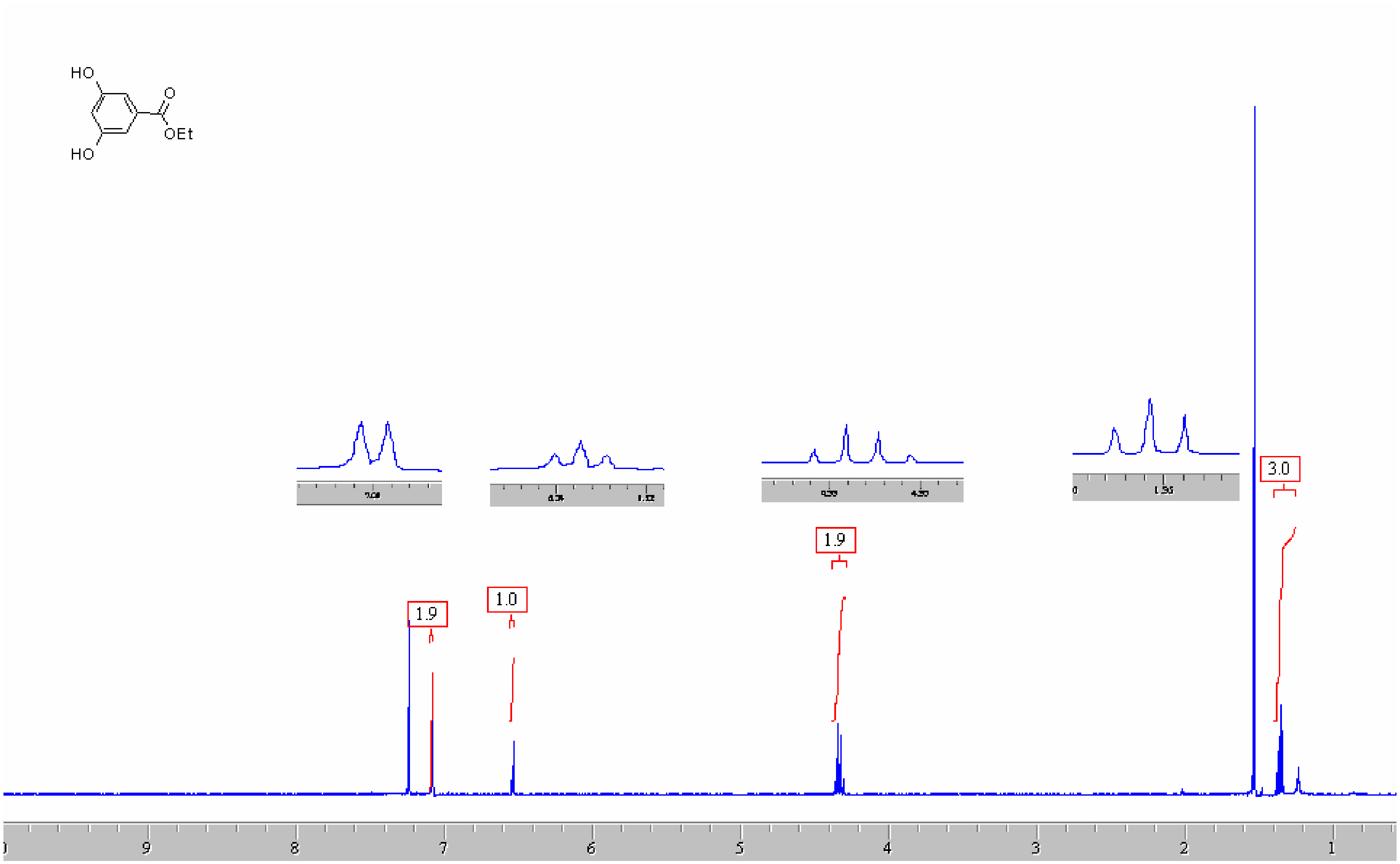
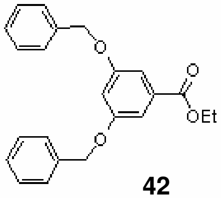


Figure A.1. ^{1}H NMR spectrum of ethyl-3,5-dihydroxybenzoate **40**



42

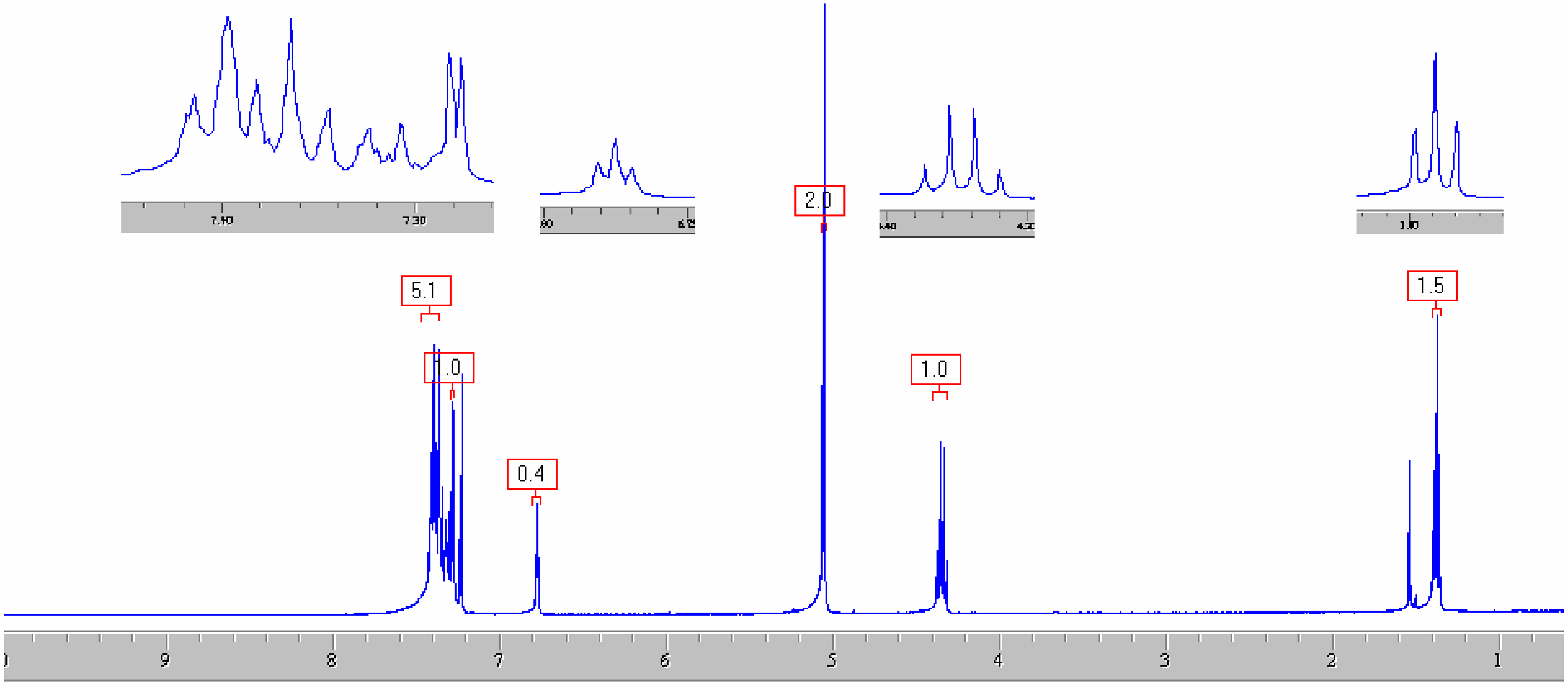


Figure A.2. ^{1}H NMR spectrum of G$_1$-ester **42**

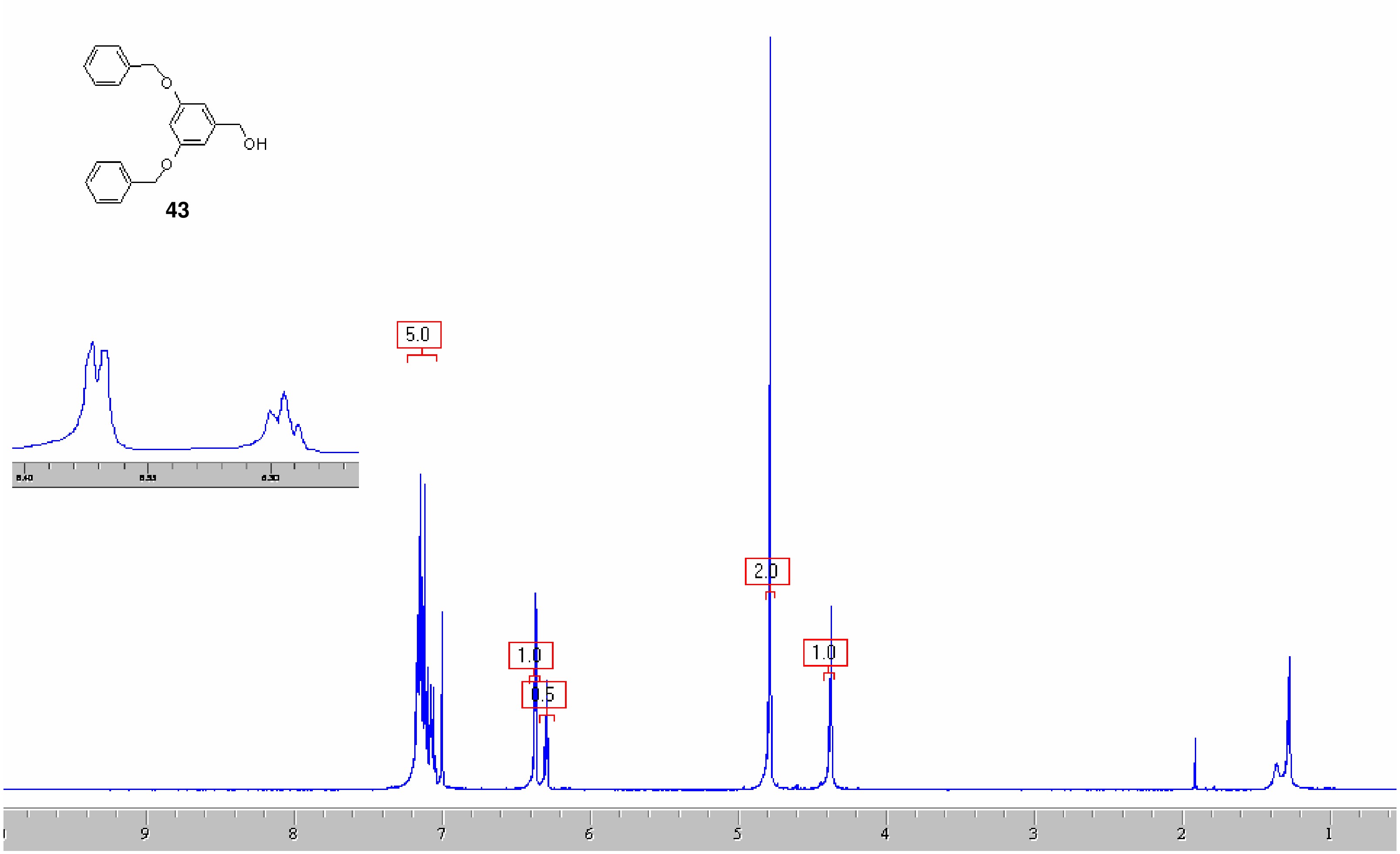


Figure A.3. ^{1}H NMR spectrum of G$_1$-alcohol **43**

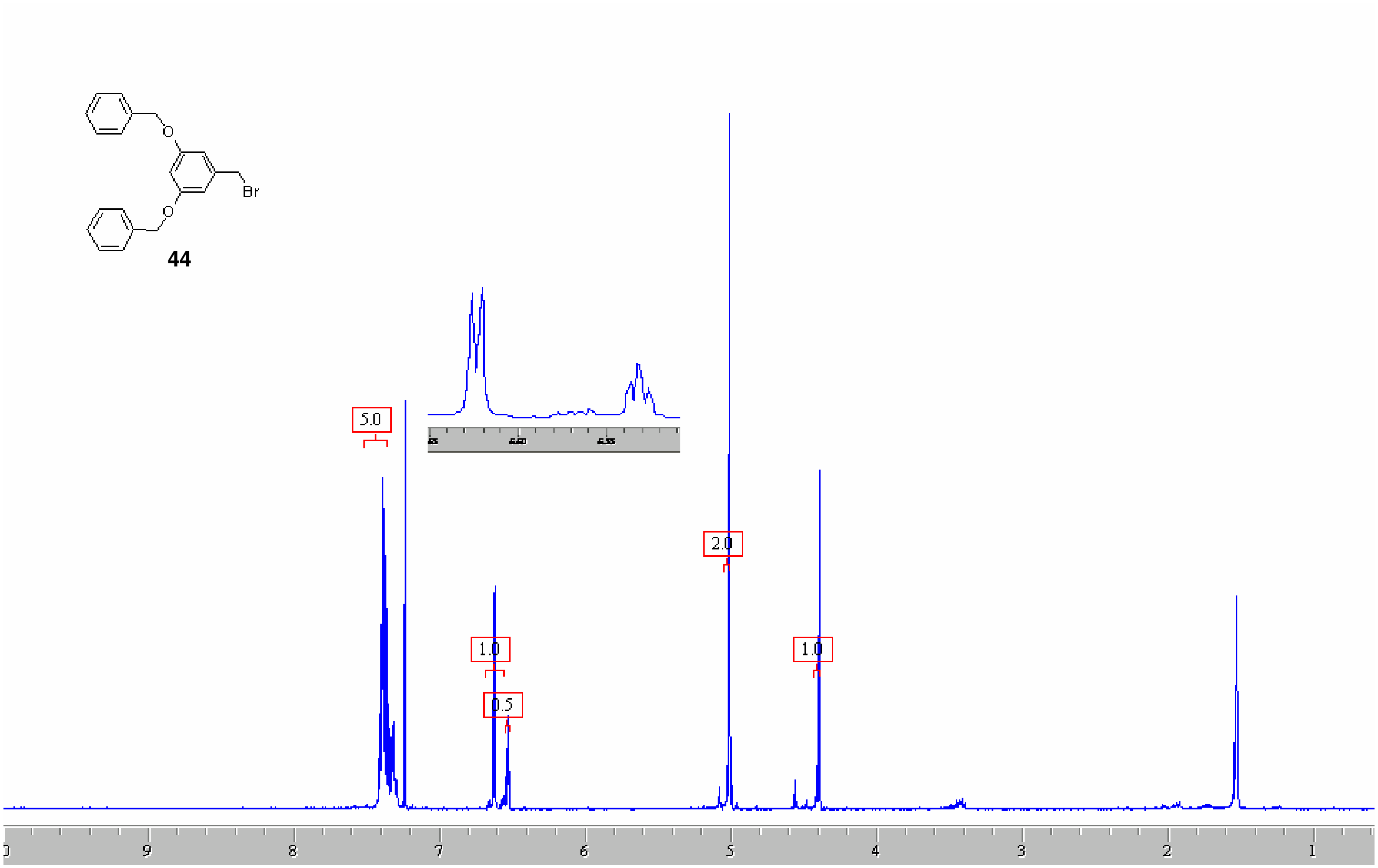


Figure A.4. ^{1}H NMR spectrum of G$_1$-bromide **44**

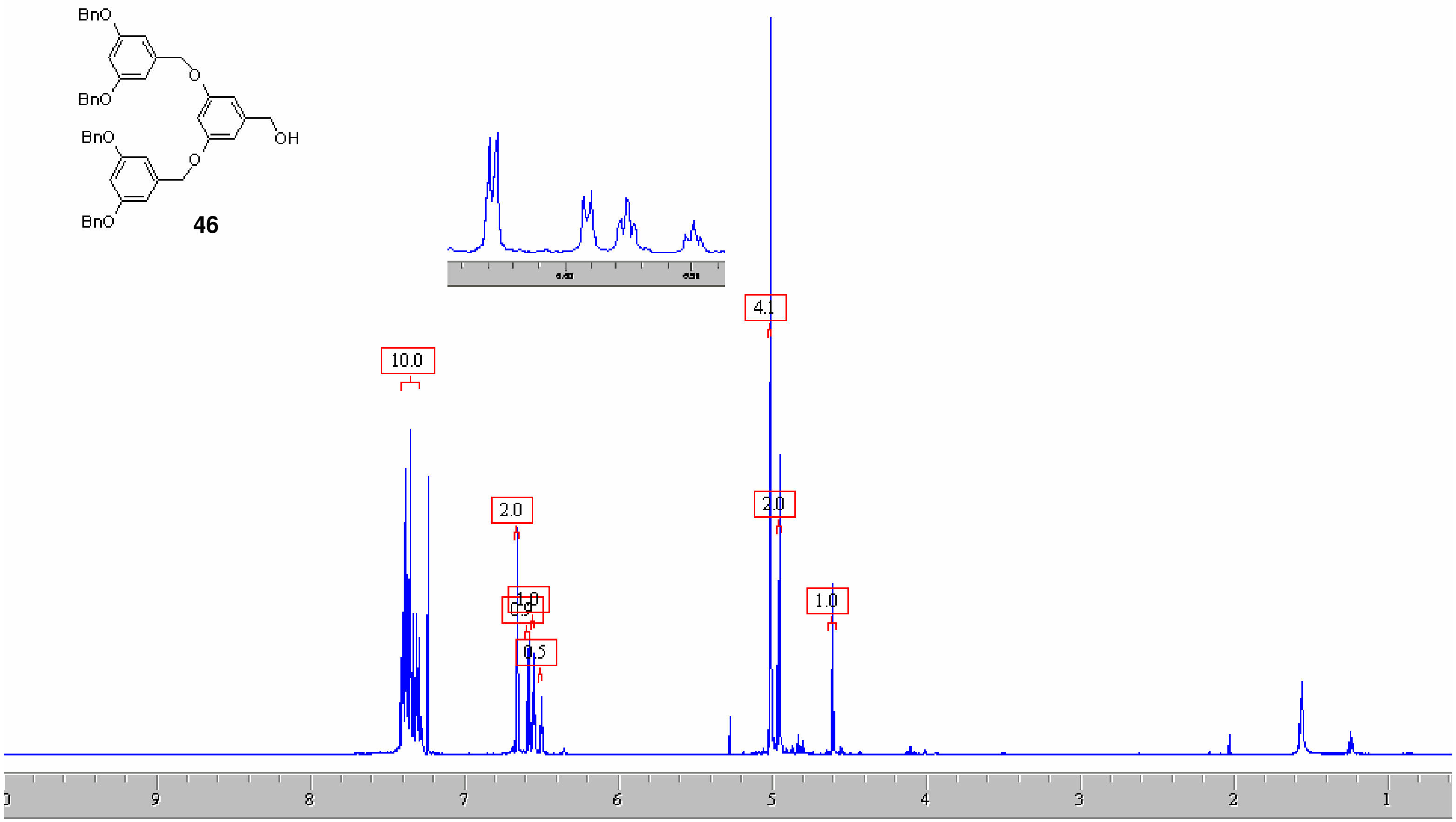


Figure A.5. ^{1}H NMR spectrum of G_2-alcohol **46**

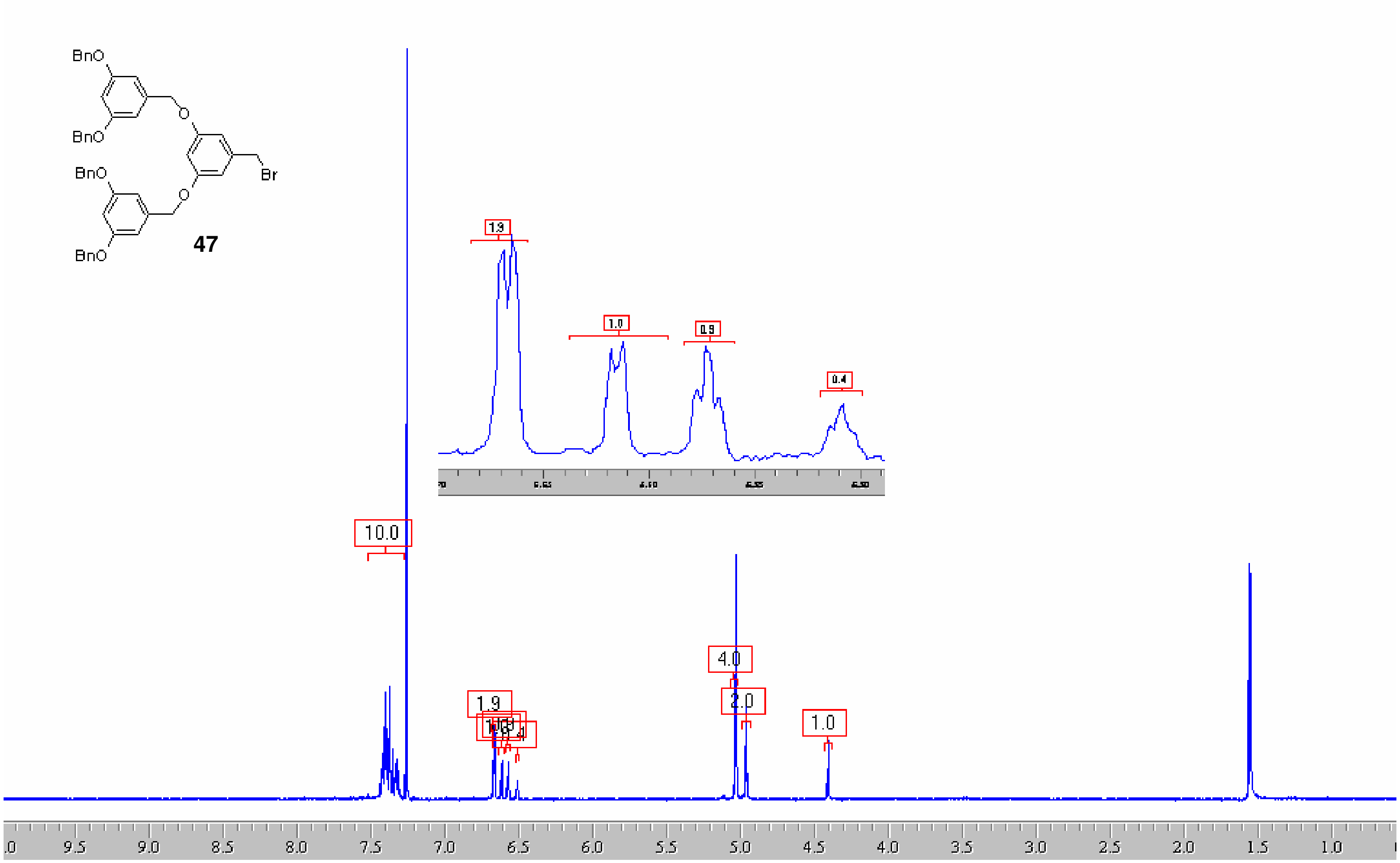


Figure A.6. ^{1}H NMR spectrum of G$_2$-bromide **47**

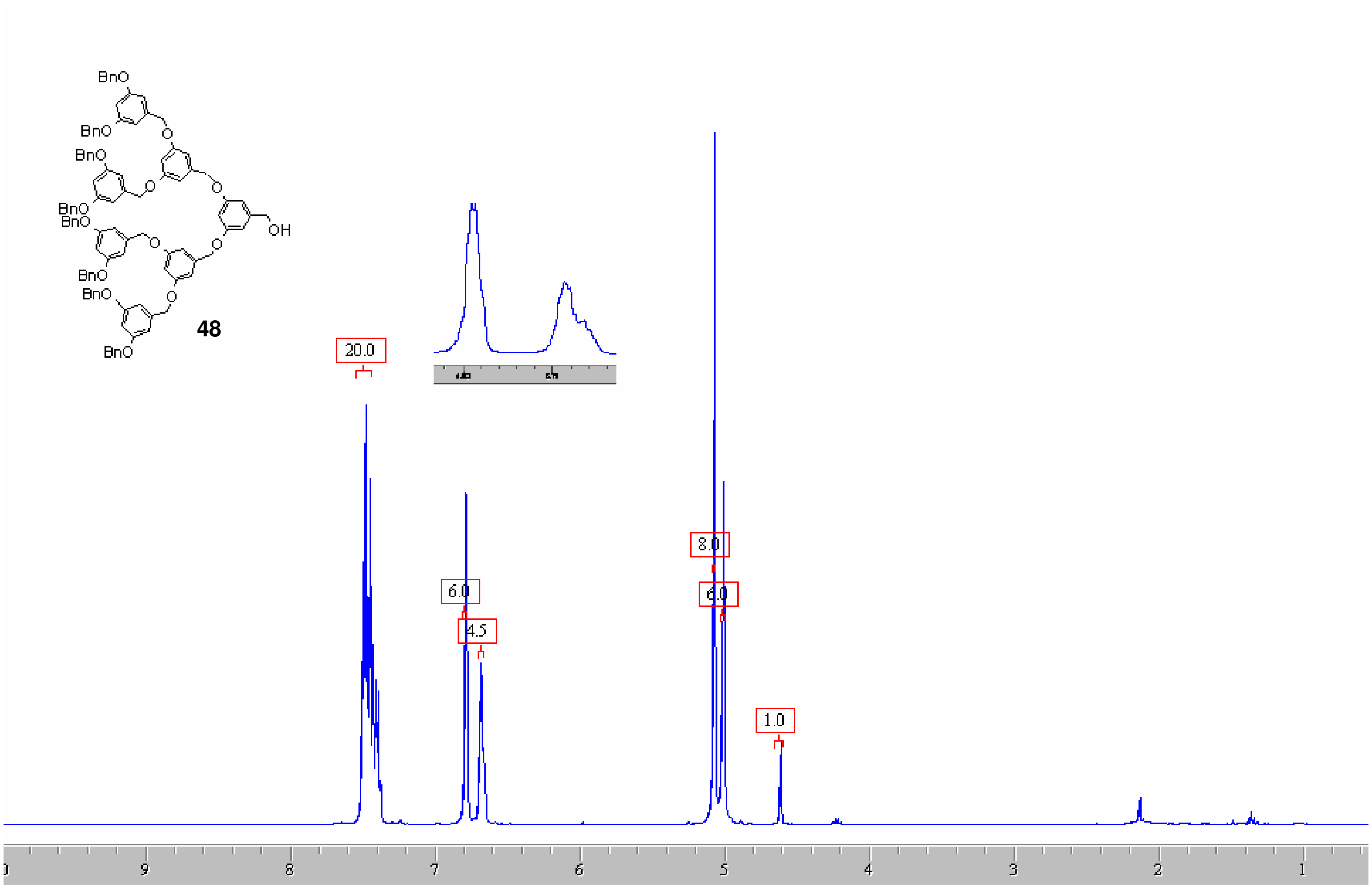


Figure A.7. ^{1}H NMR spectrum of G$_3$-alcohol **48**

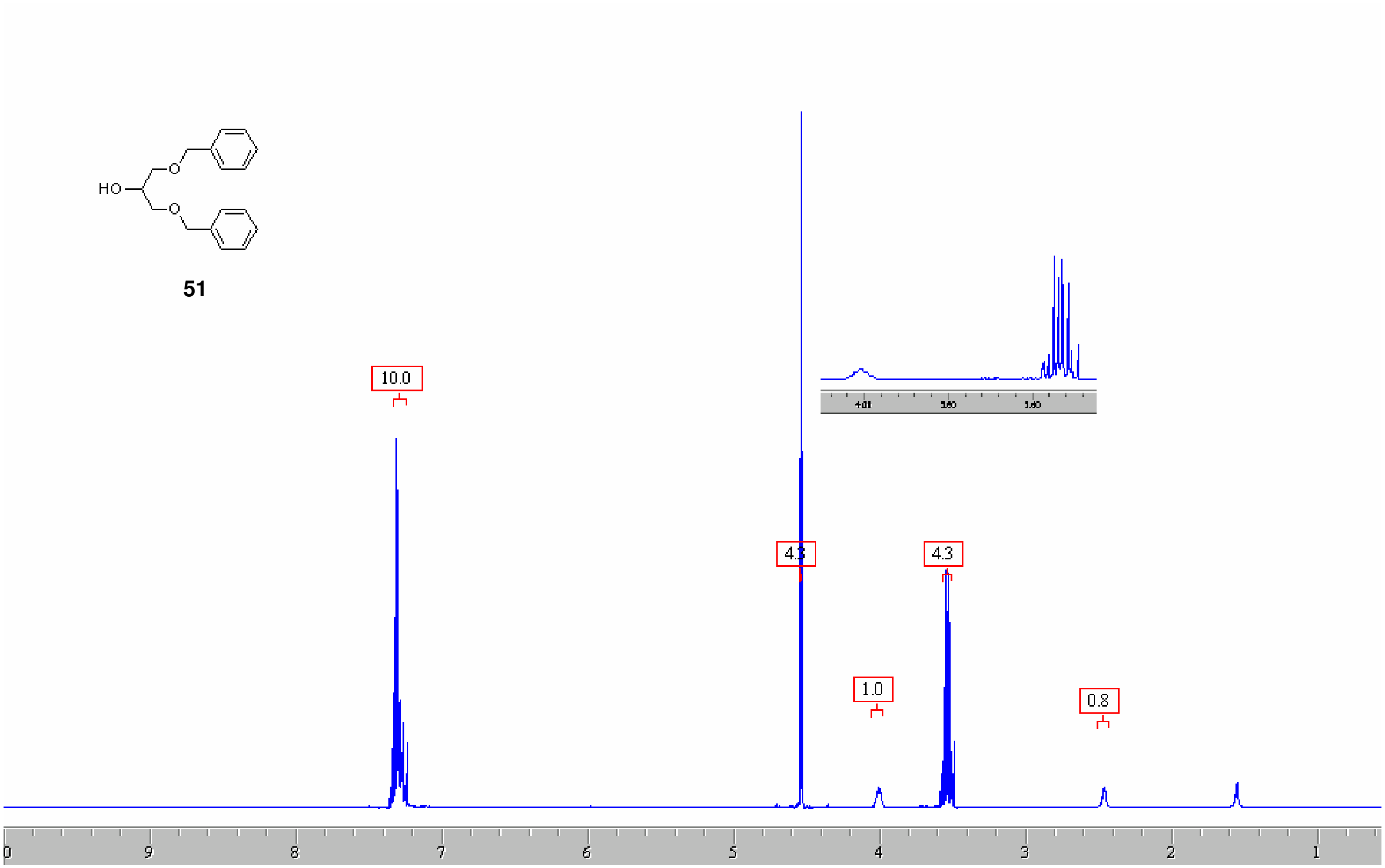


Figure A.8. ^{1}H NMR spectrum of G$_1$-alcohol **51**

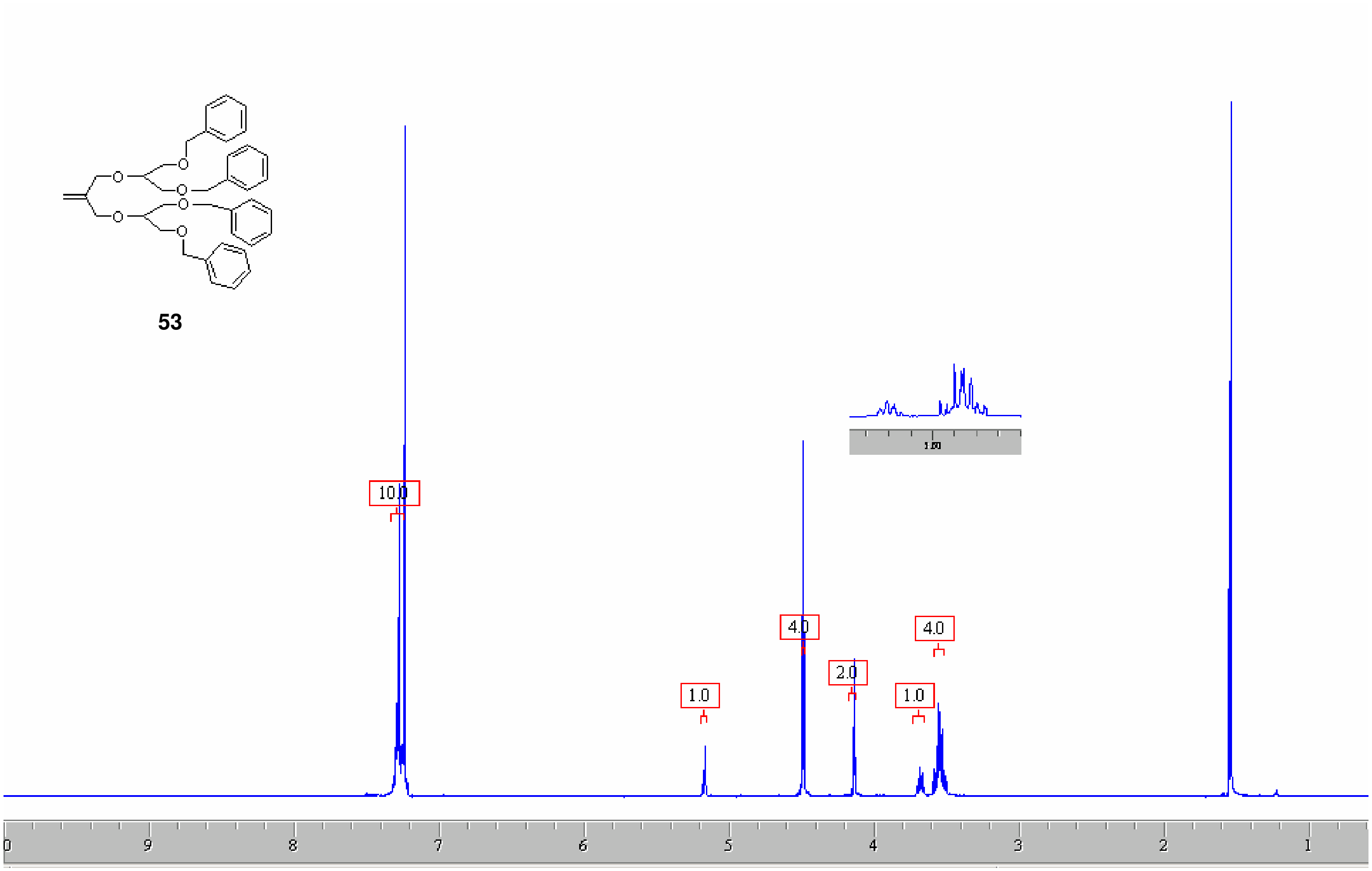


Figure A.9. ^{1}H NMR spectrum of G$_2$-ene **53**

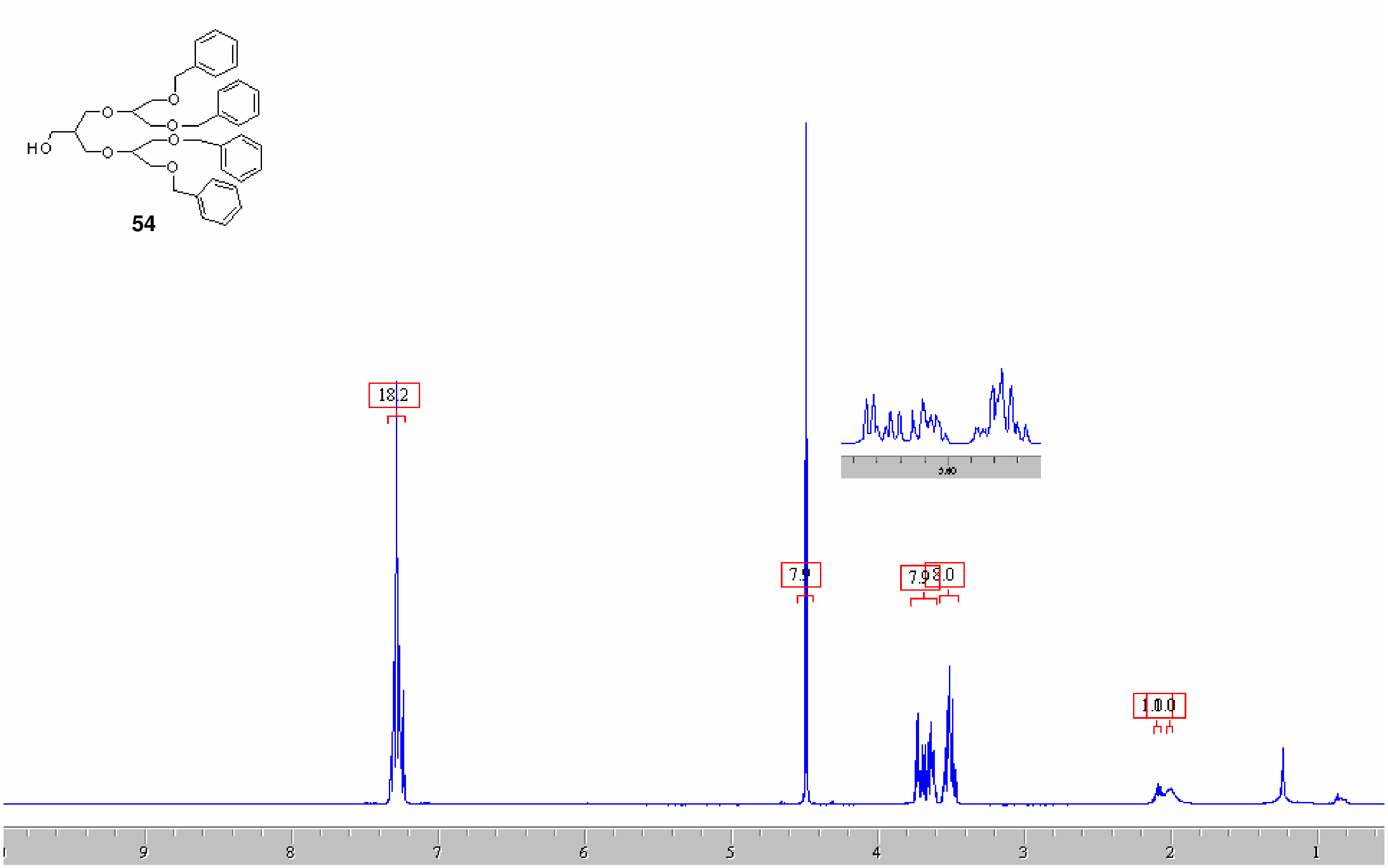


Figure A.10. ^{1}H NMR spectrum of G$_2$-ol **54**

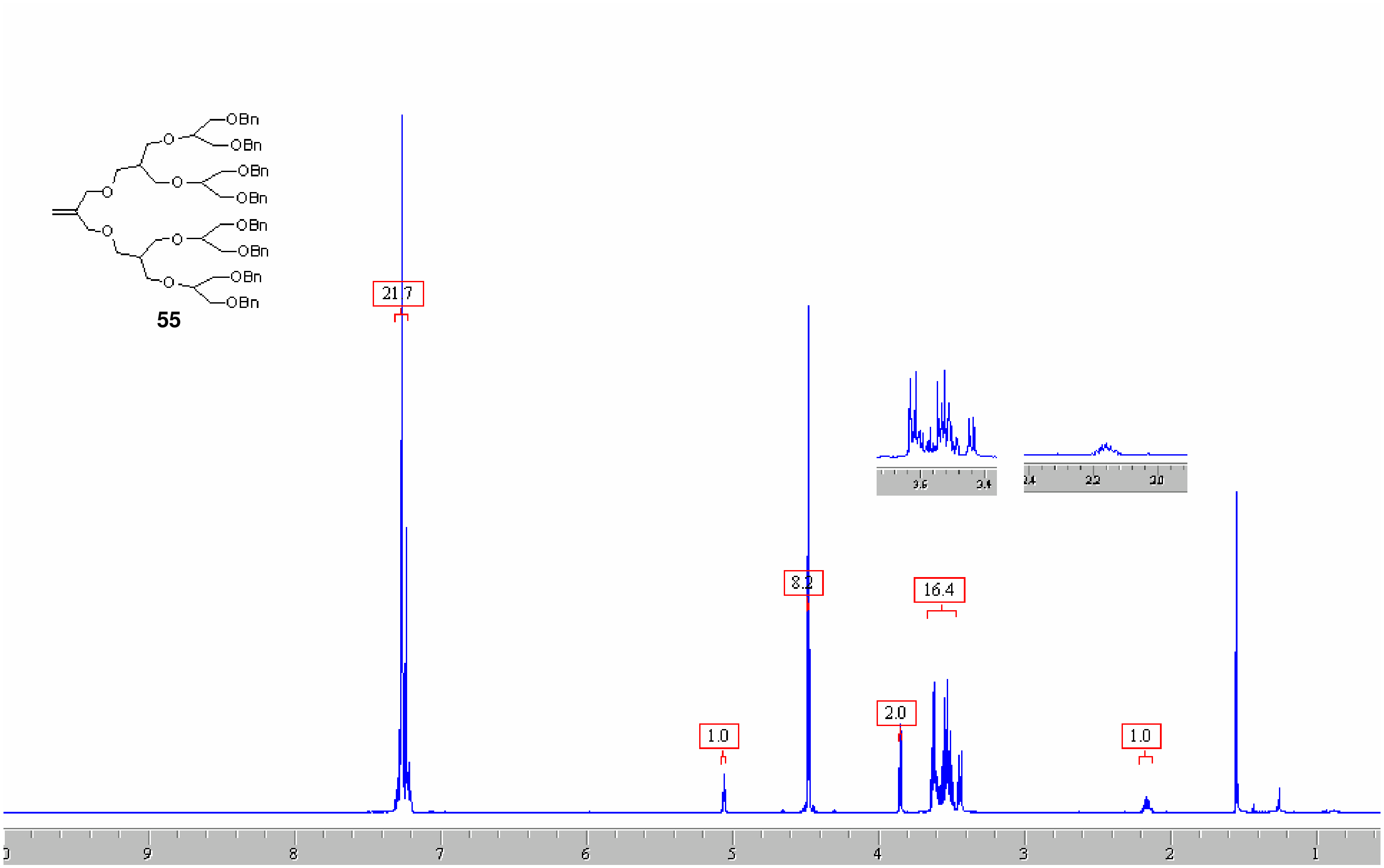


Figure A.11. ^{1}H NMR spectrum of G$_3$-ene **55**

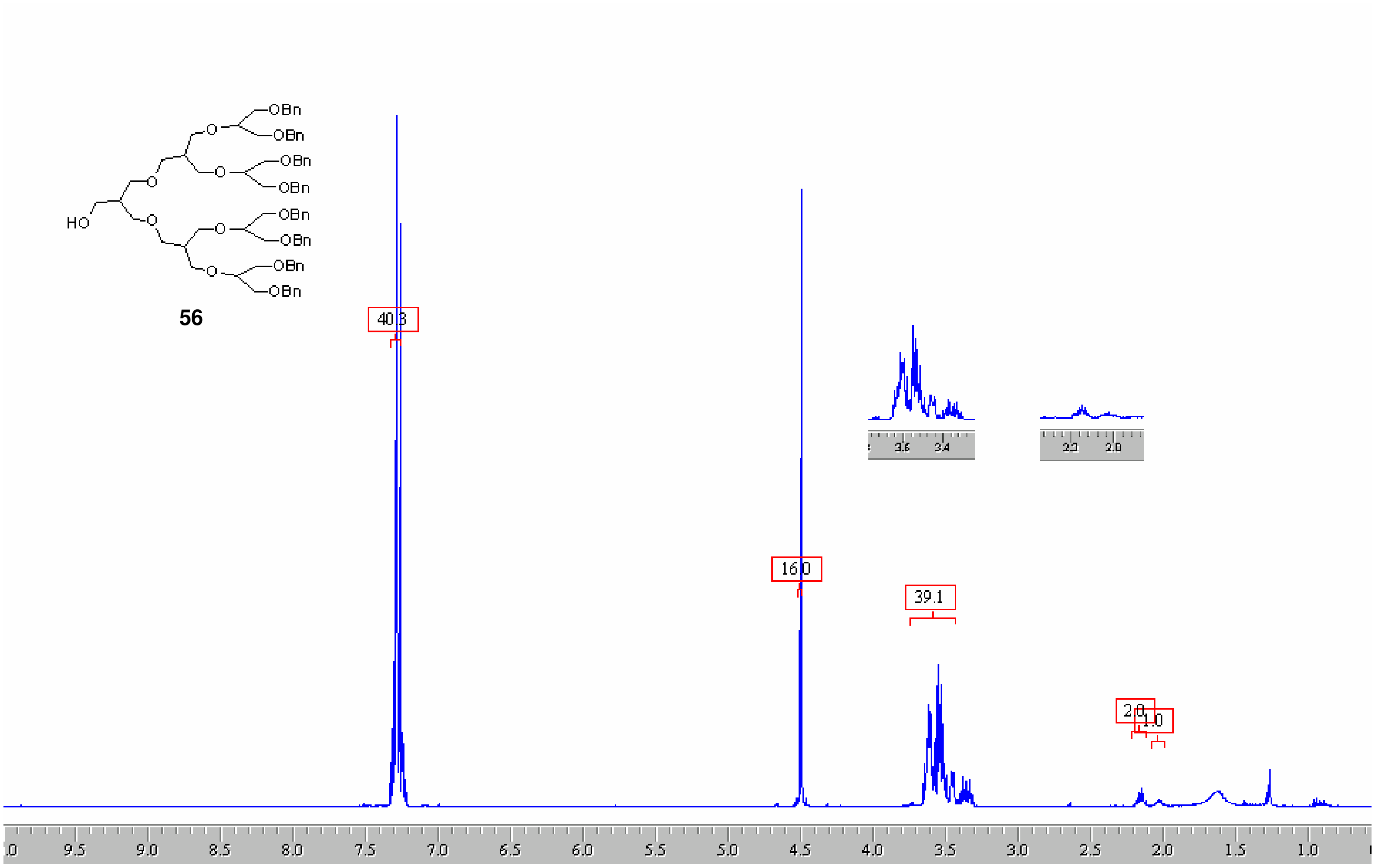


Figure A.12. ^{1}H NMR spectrum of G_3-alcohol **56**

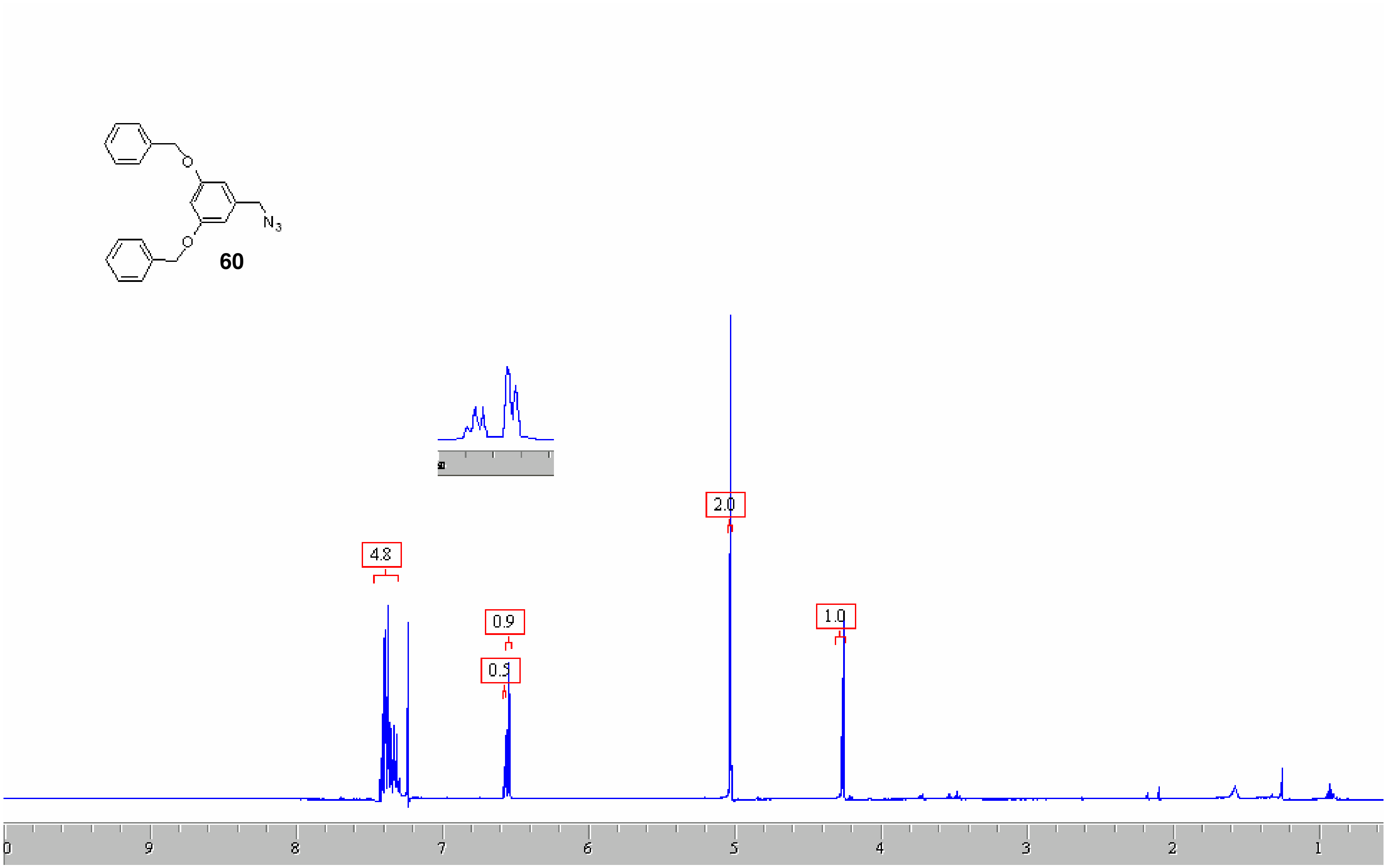


Figure A.13. ^{1}H NMR spectrum of G$_1$-azide **60**

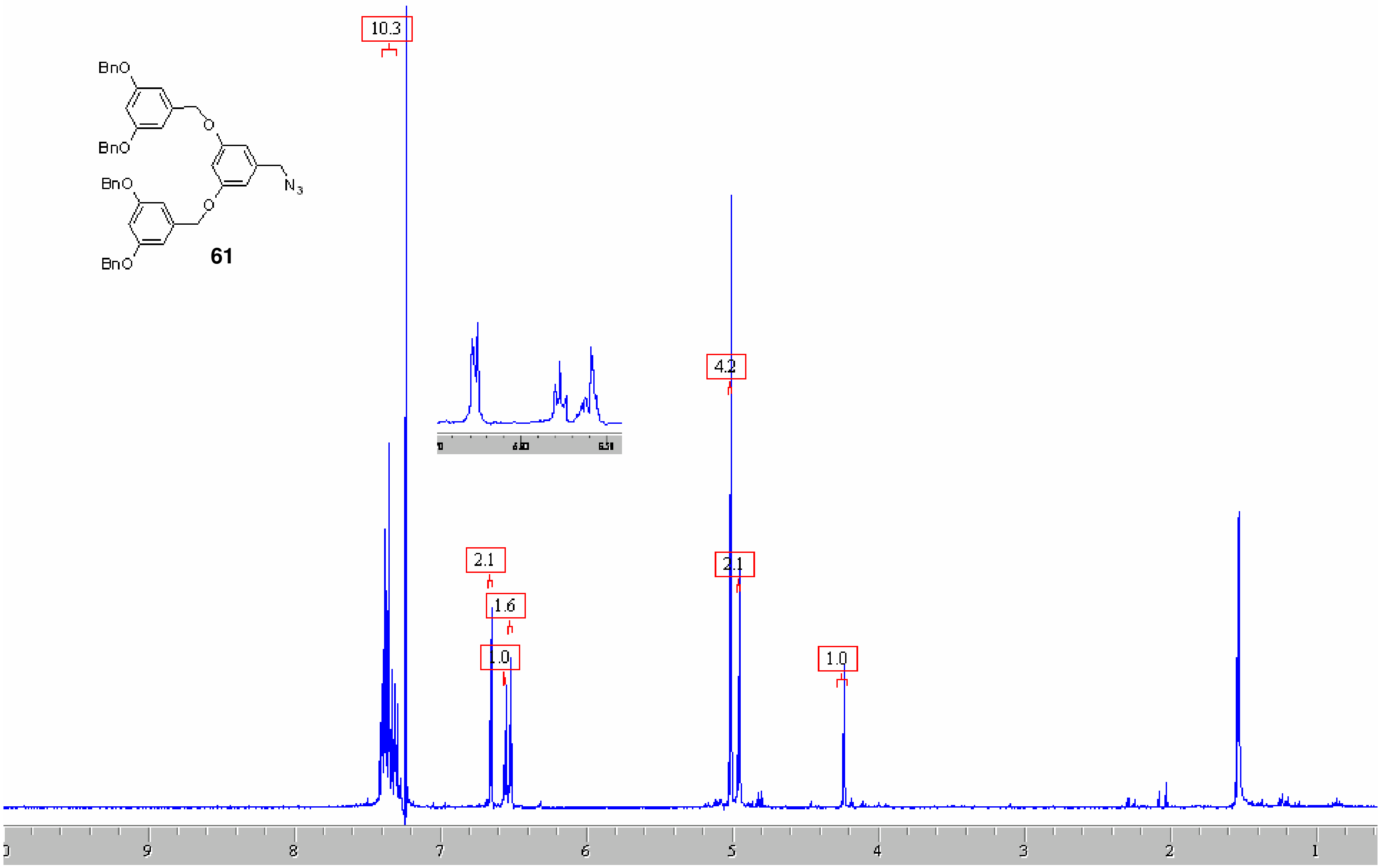


Figure A.14. ^{1}H NMR spectrum of G$_2$-azide **61**

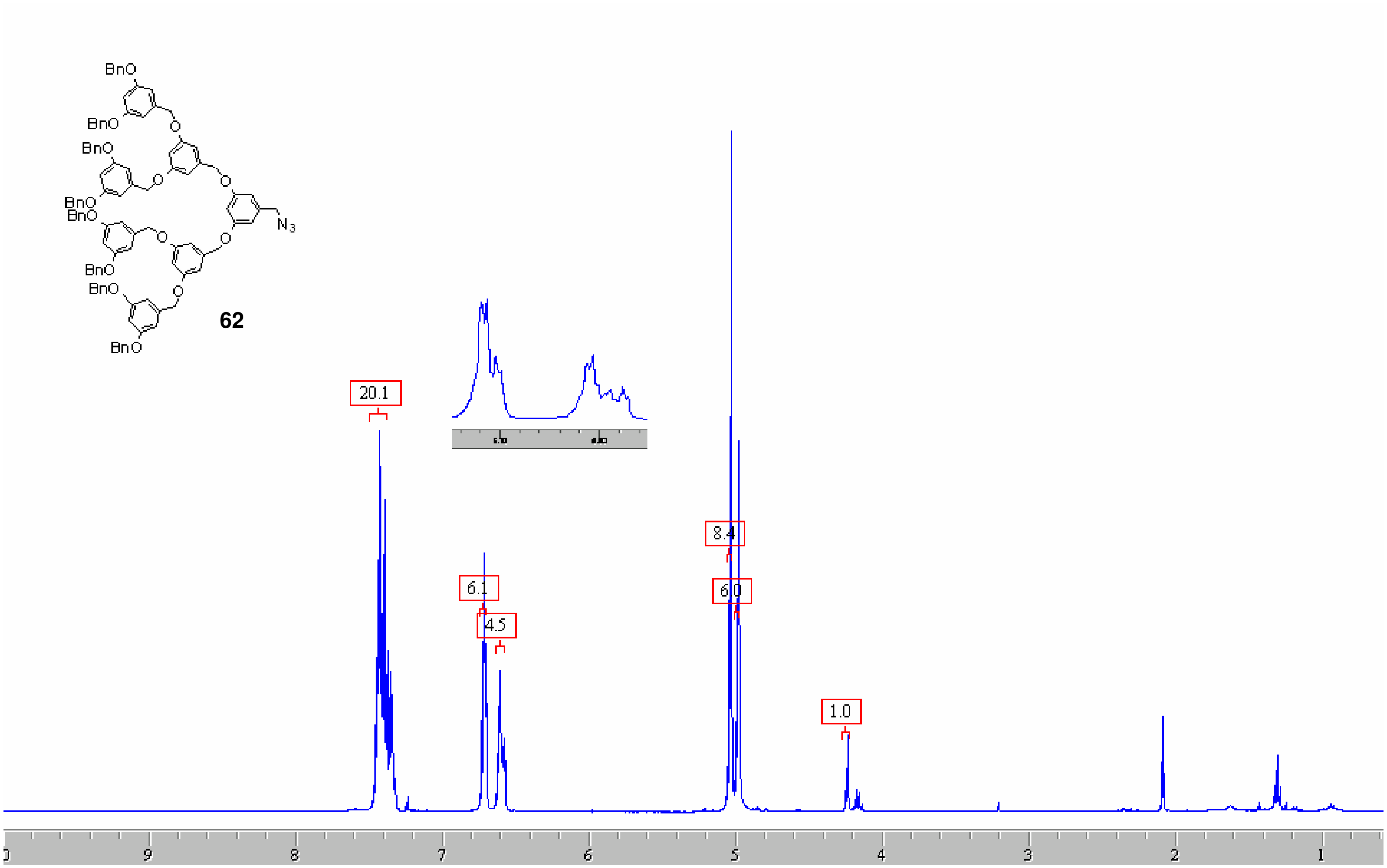


Figure A.15. ^{1}H NMR spectrum of G_3-azide **62**

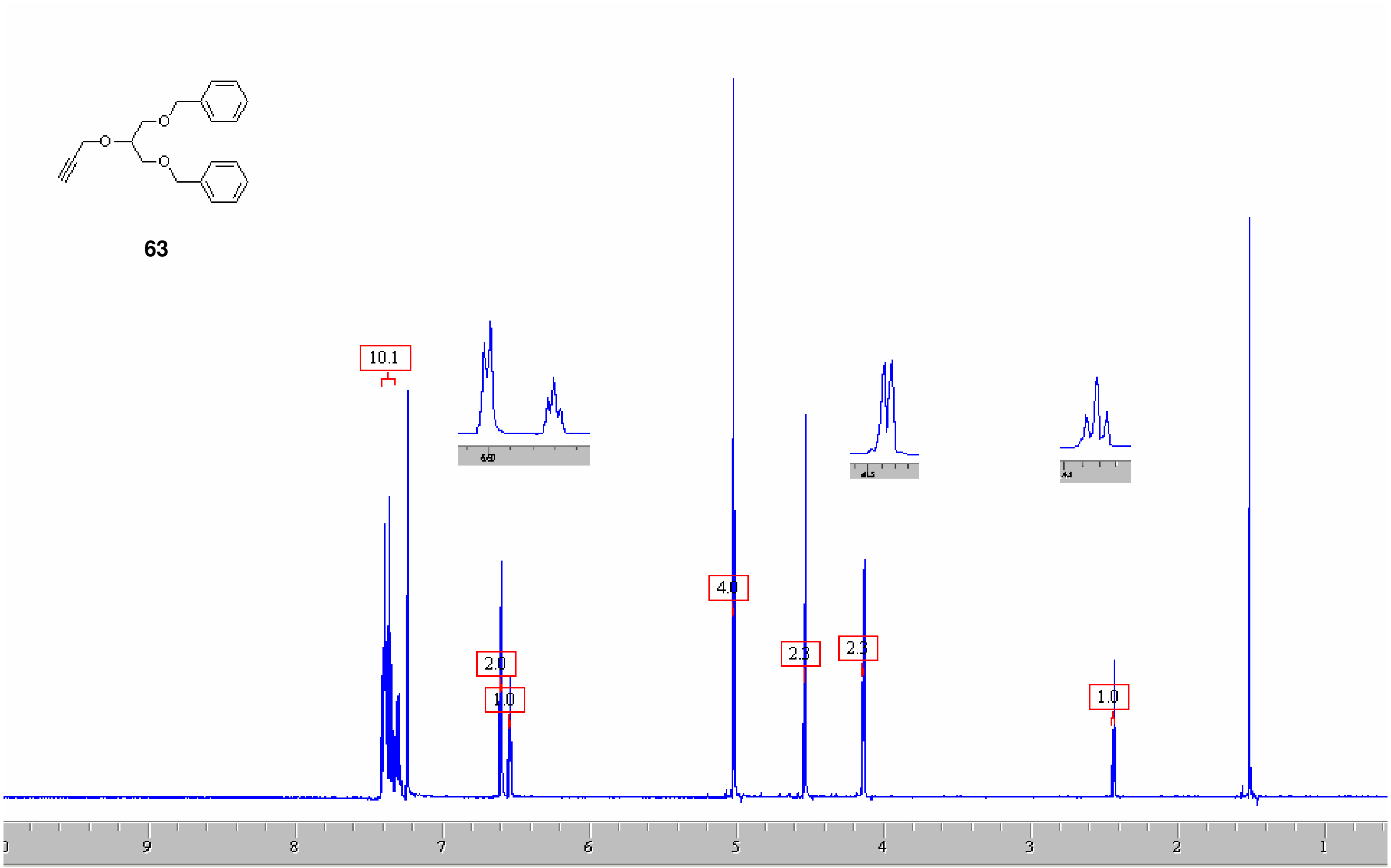


Figure A.16 ^{1}H NMR spectrum of G$_1$-acetylene **63**

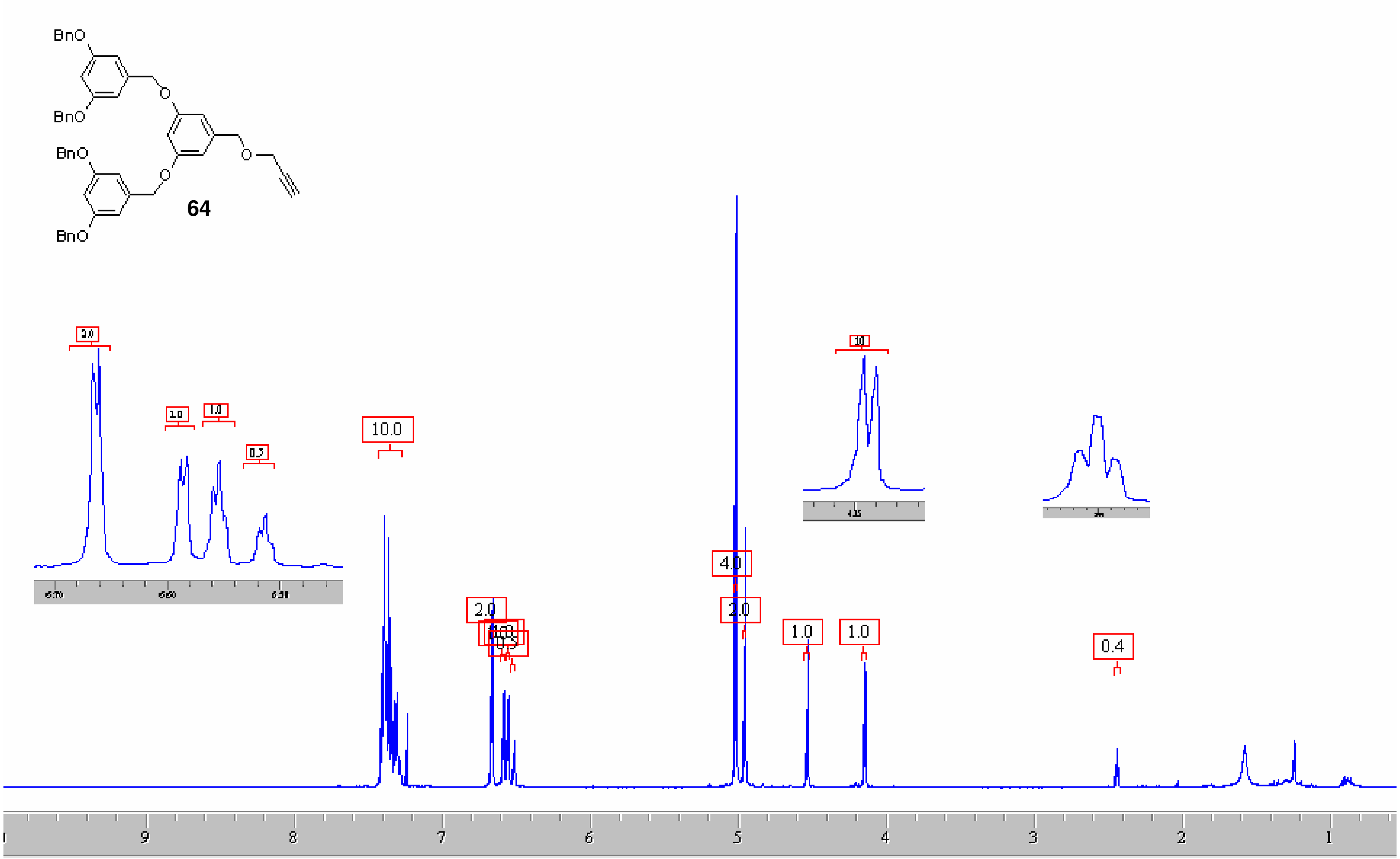


Figure A.17. ^{1}H NMR spectrum of G$_2$-acetylene **64**

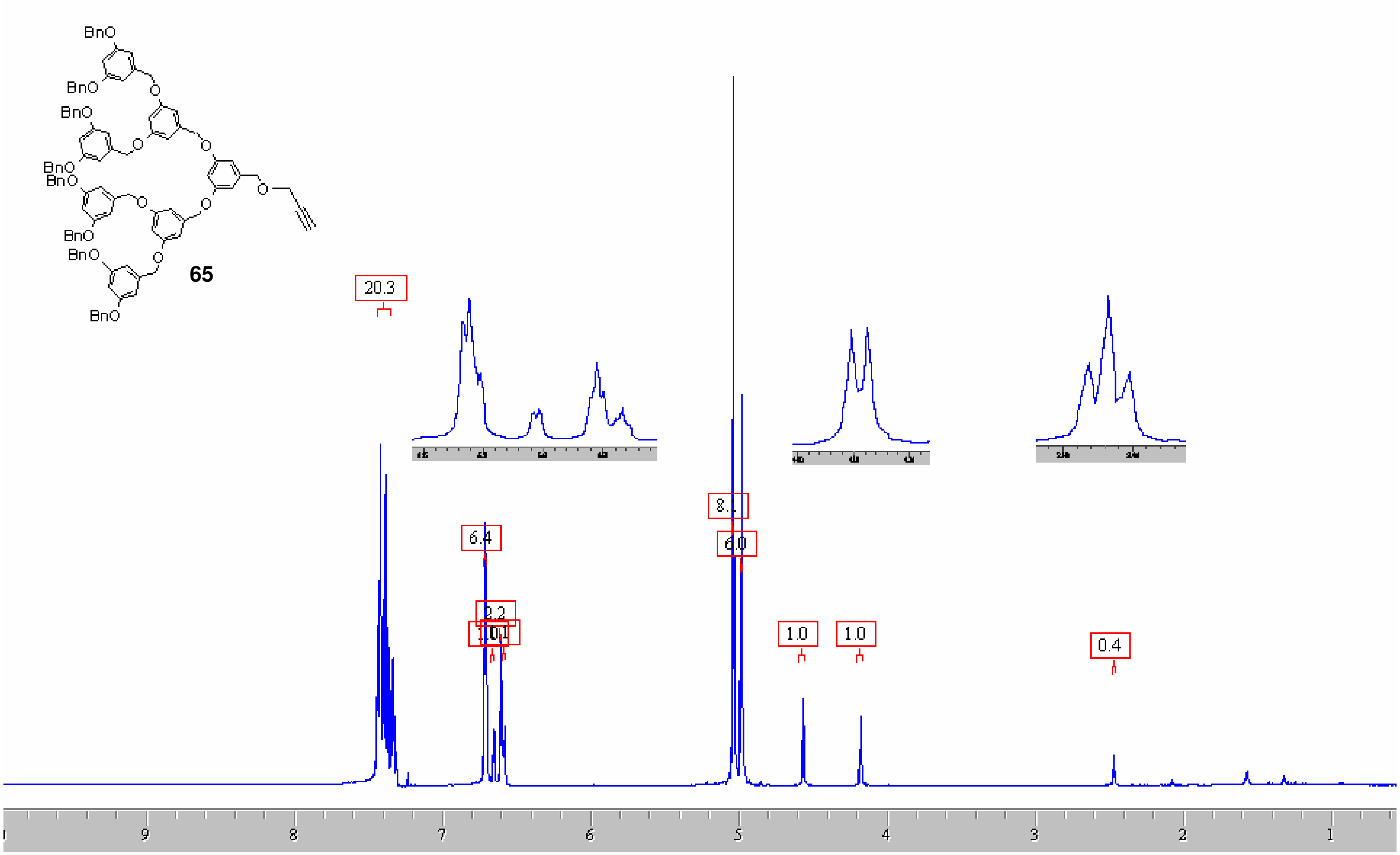


Figure A.18. ^{1}H NMR spectrum of G_3-acetylene **65**

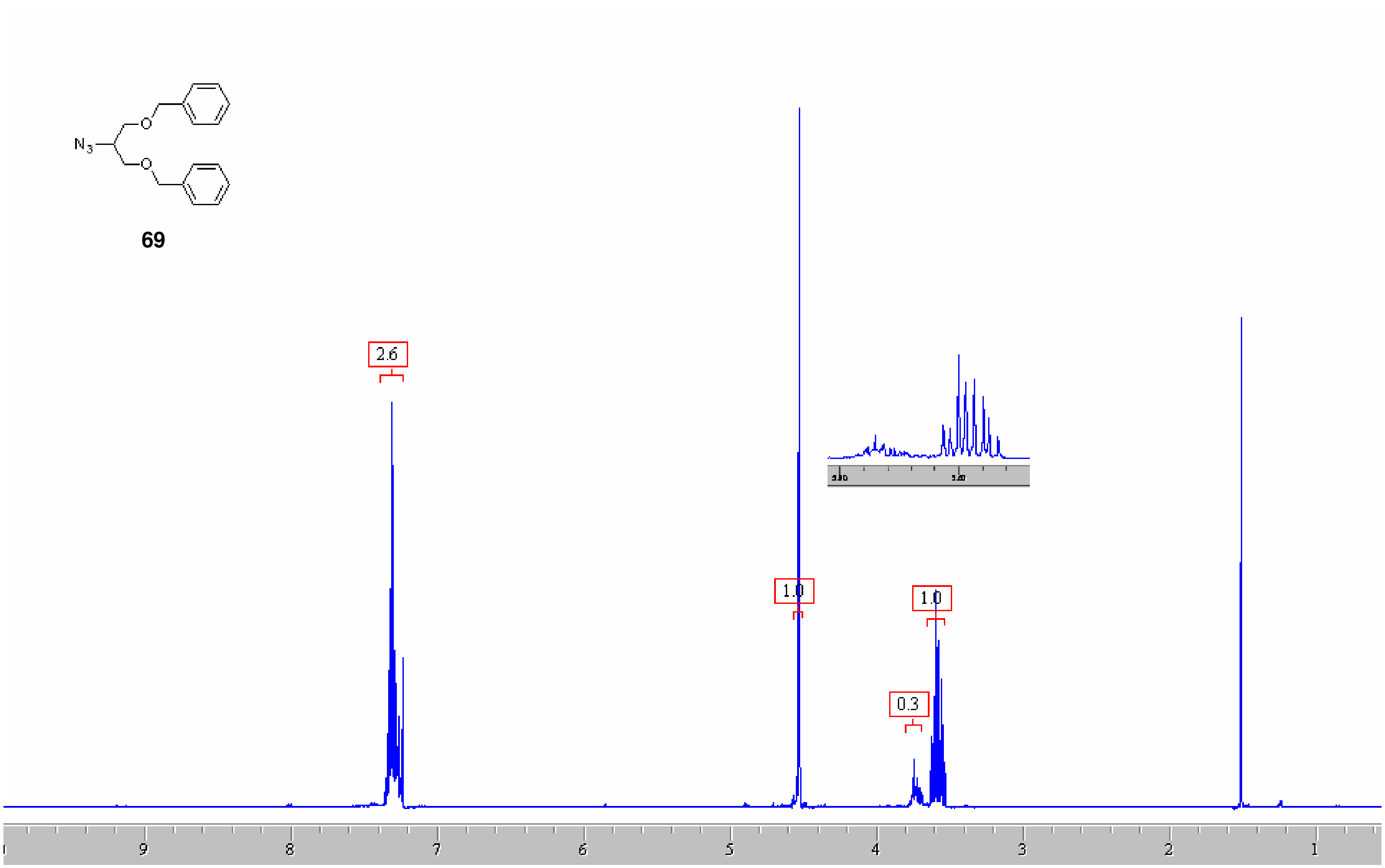


Figure A.19. ^{1}H NMR spectrum of G$_1$-azide **69**

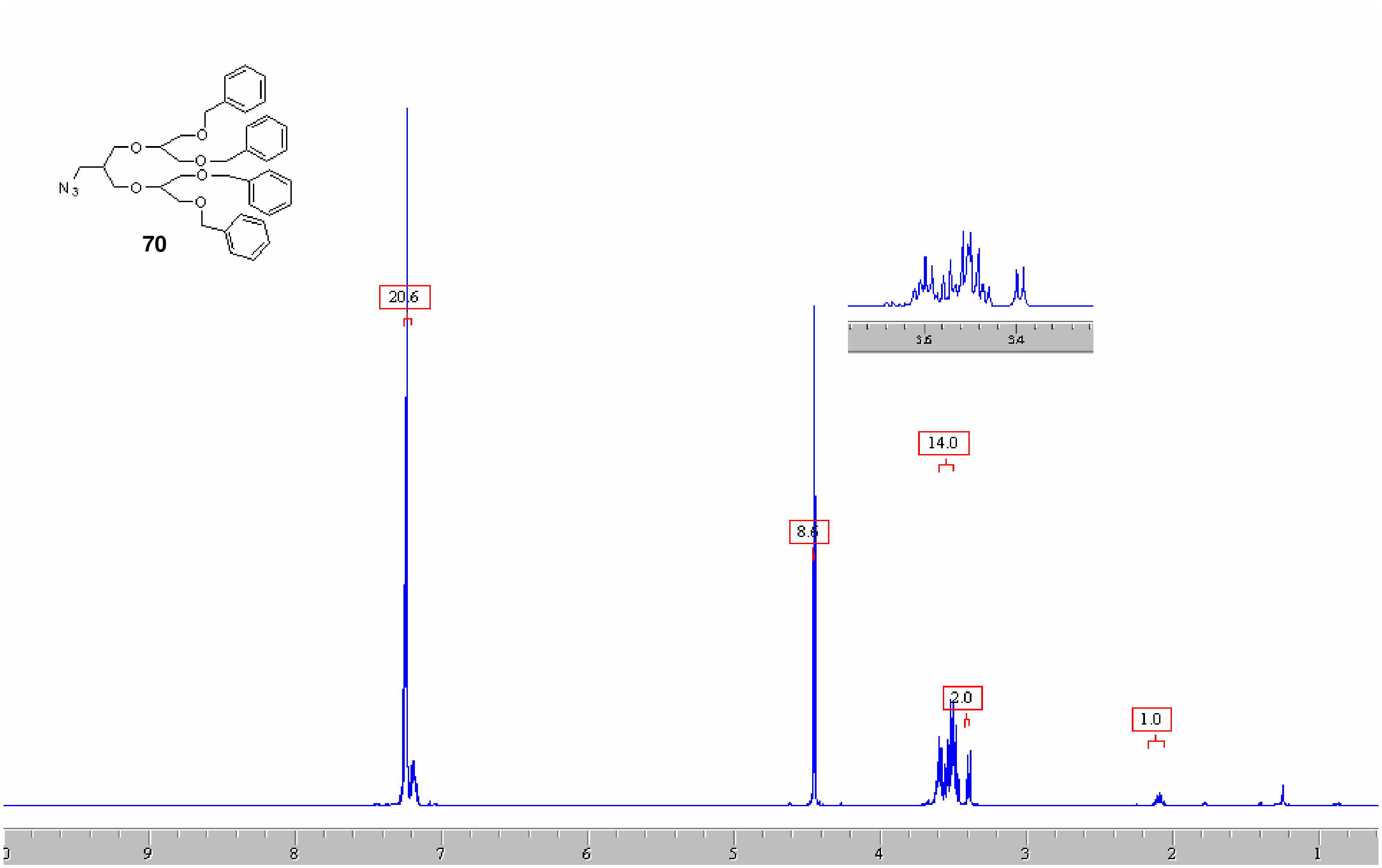


Figure A.20. ^{1}H NMR spectrum of G$_2$-azide **70**

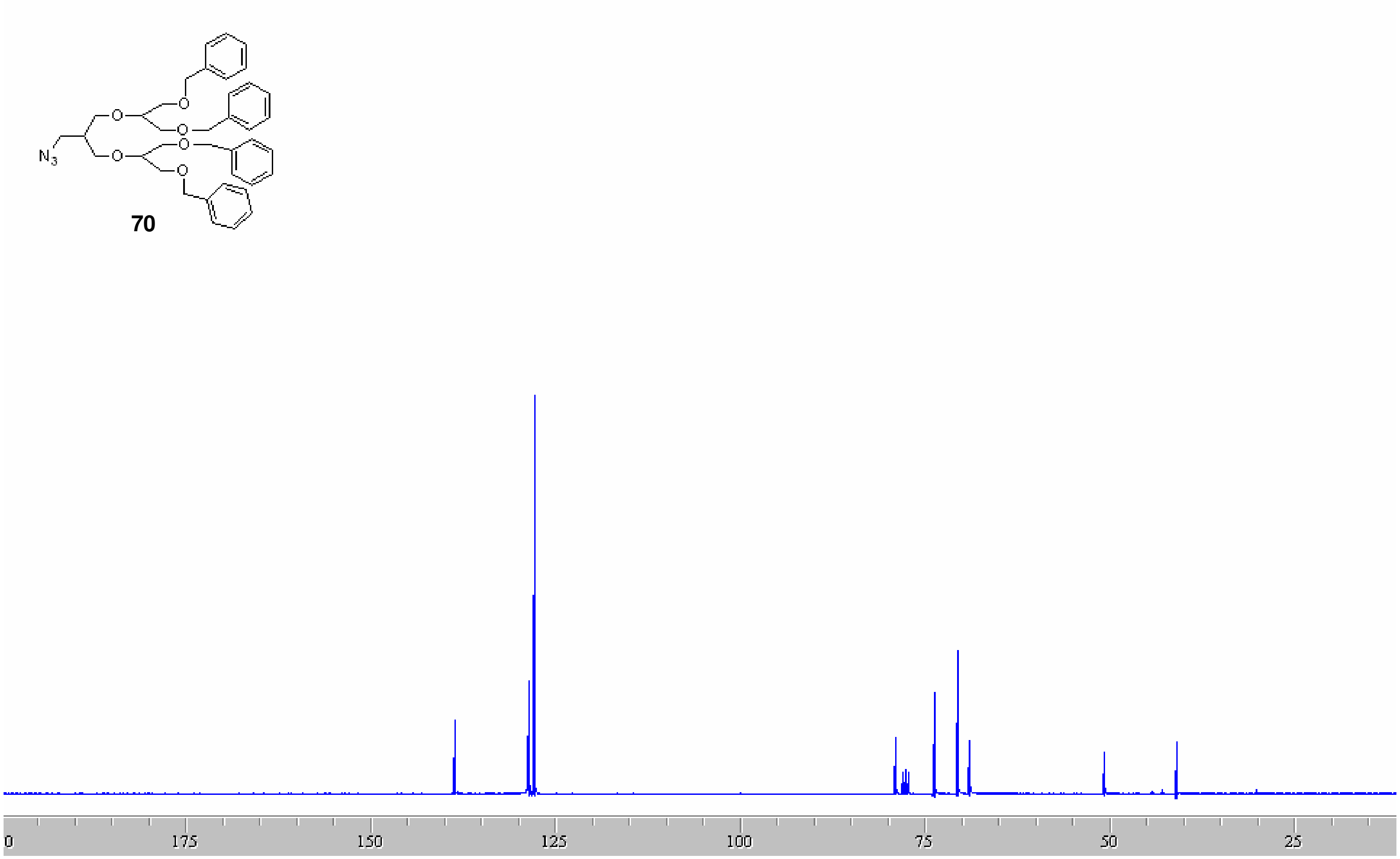


Figure A.21. ^{13}C NMR spectrum of G_2-azide **70**

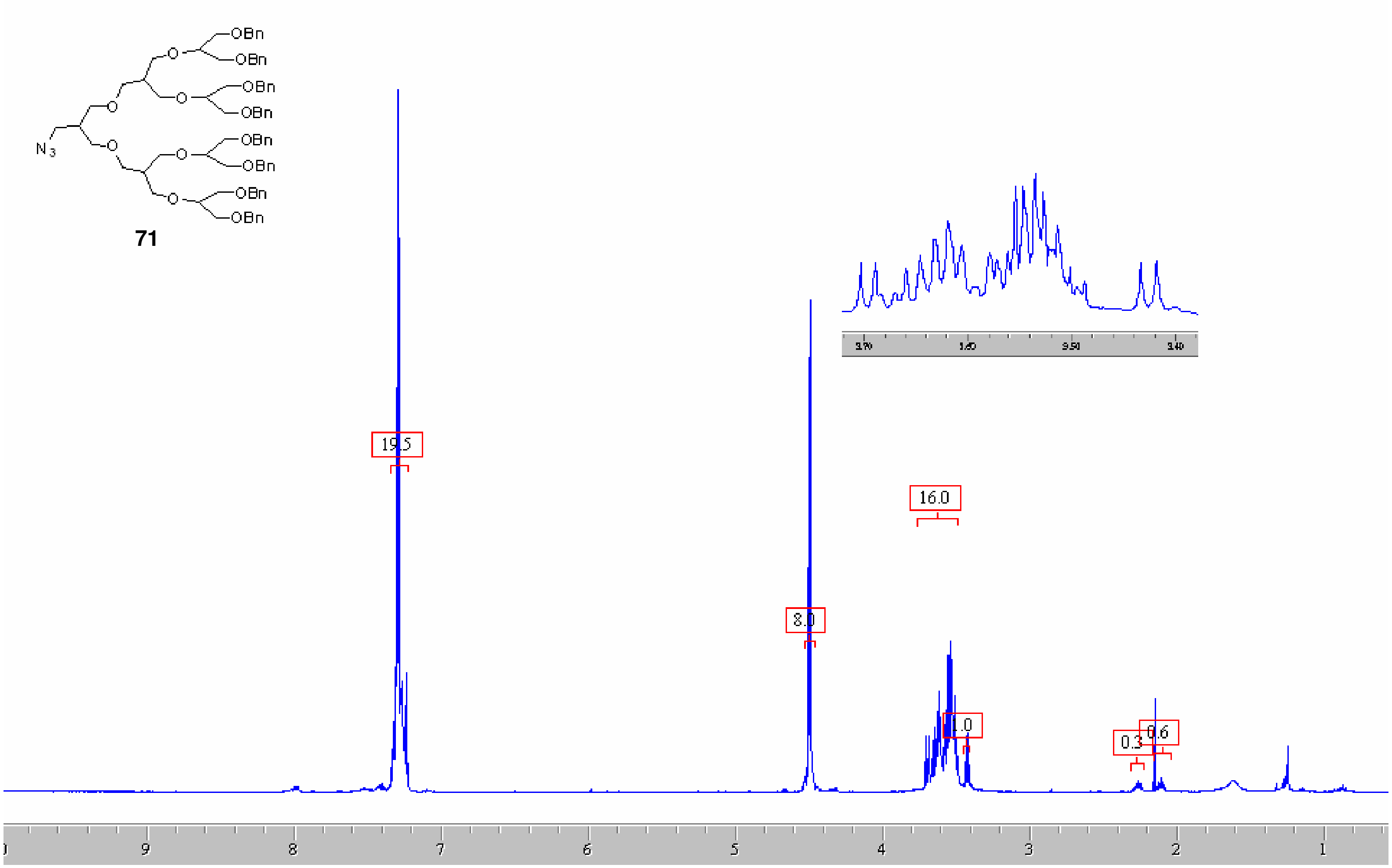


Figure A.22. ^{1}H NMR spectrum of G_3-azide **71**

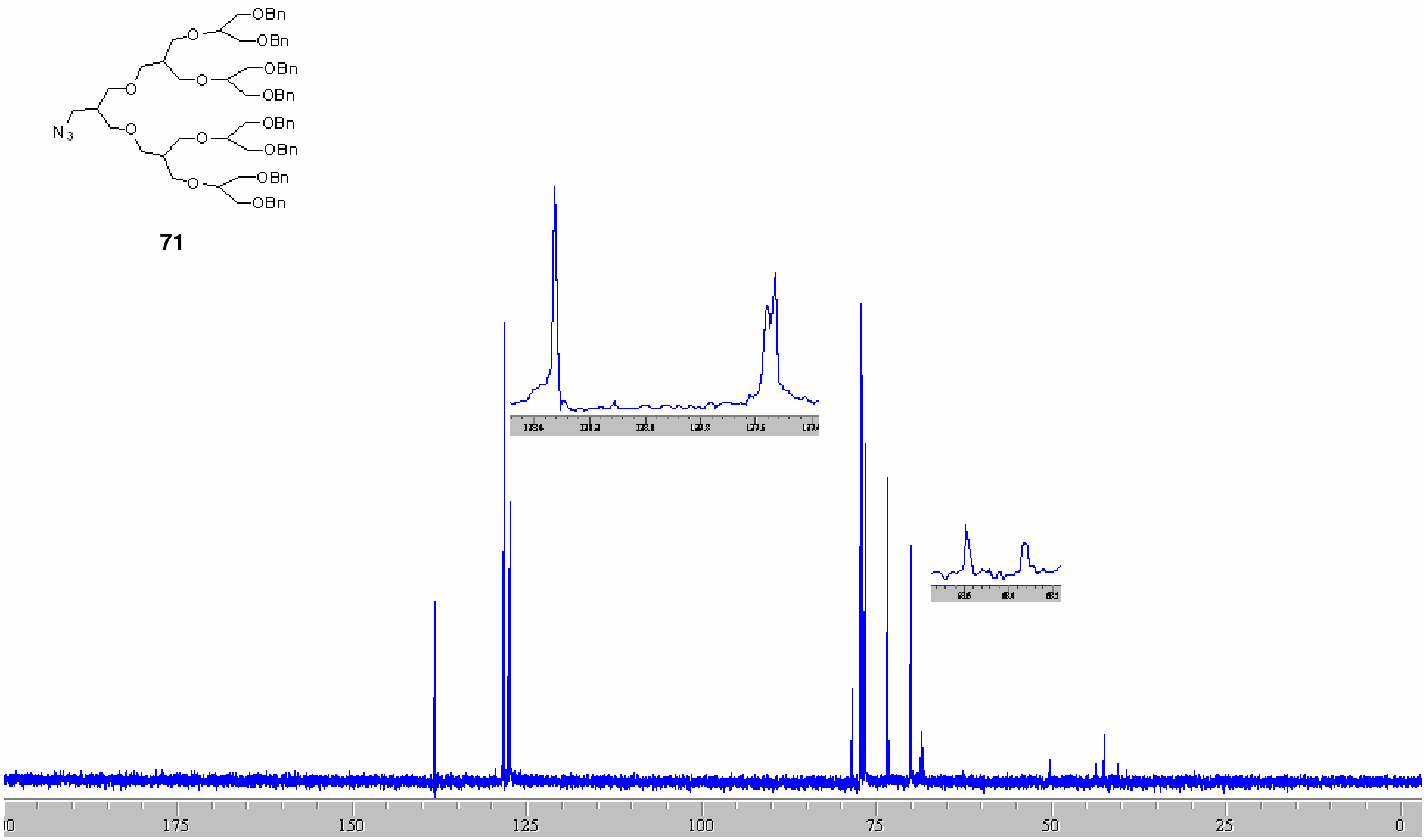


Figure A.23. ^{13}C NMR spectrum of G$_3$-azide **71**

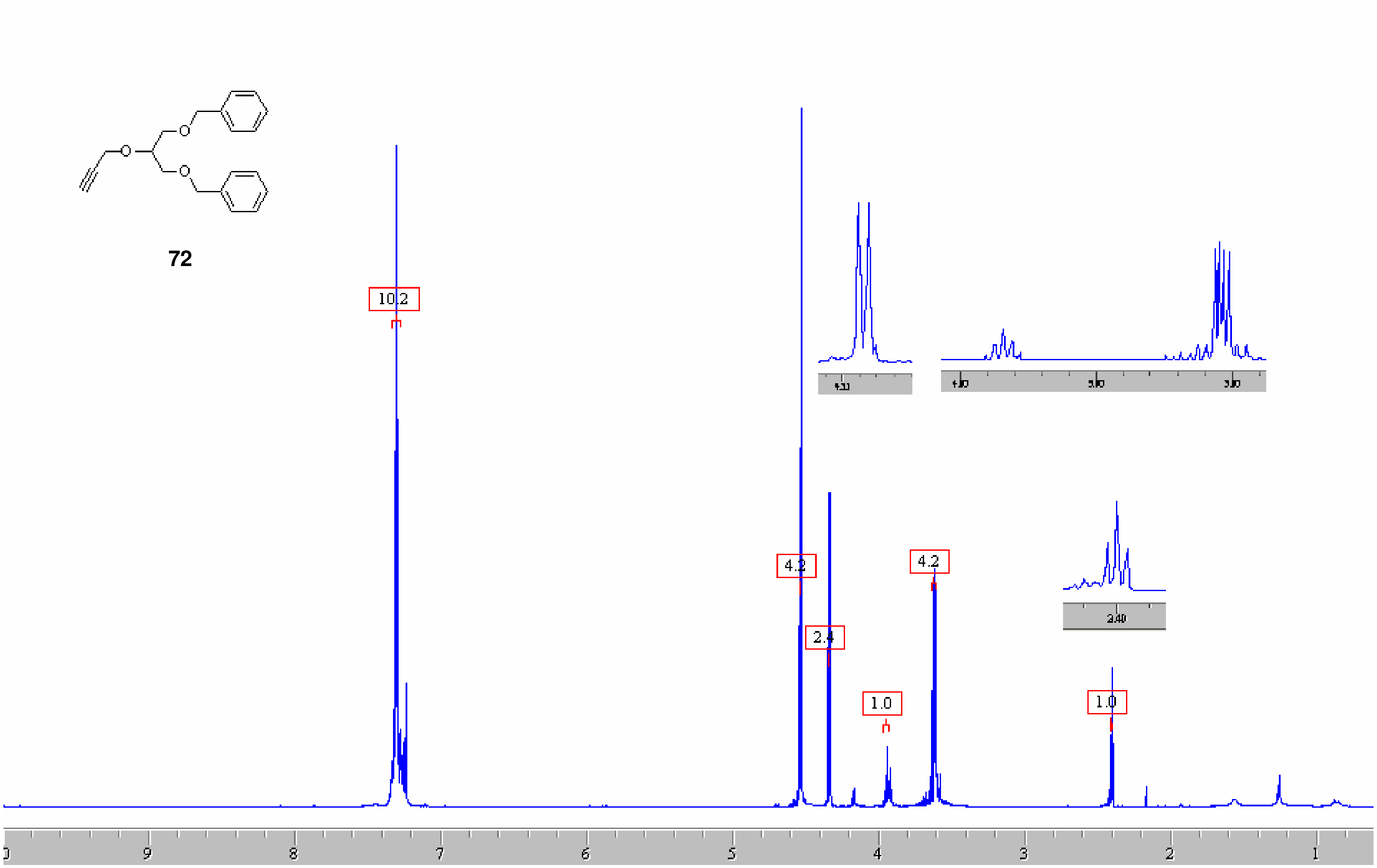


Figure A.24. ^{1}H NMR spectrum of G$_1$-acetylene **72**

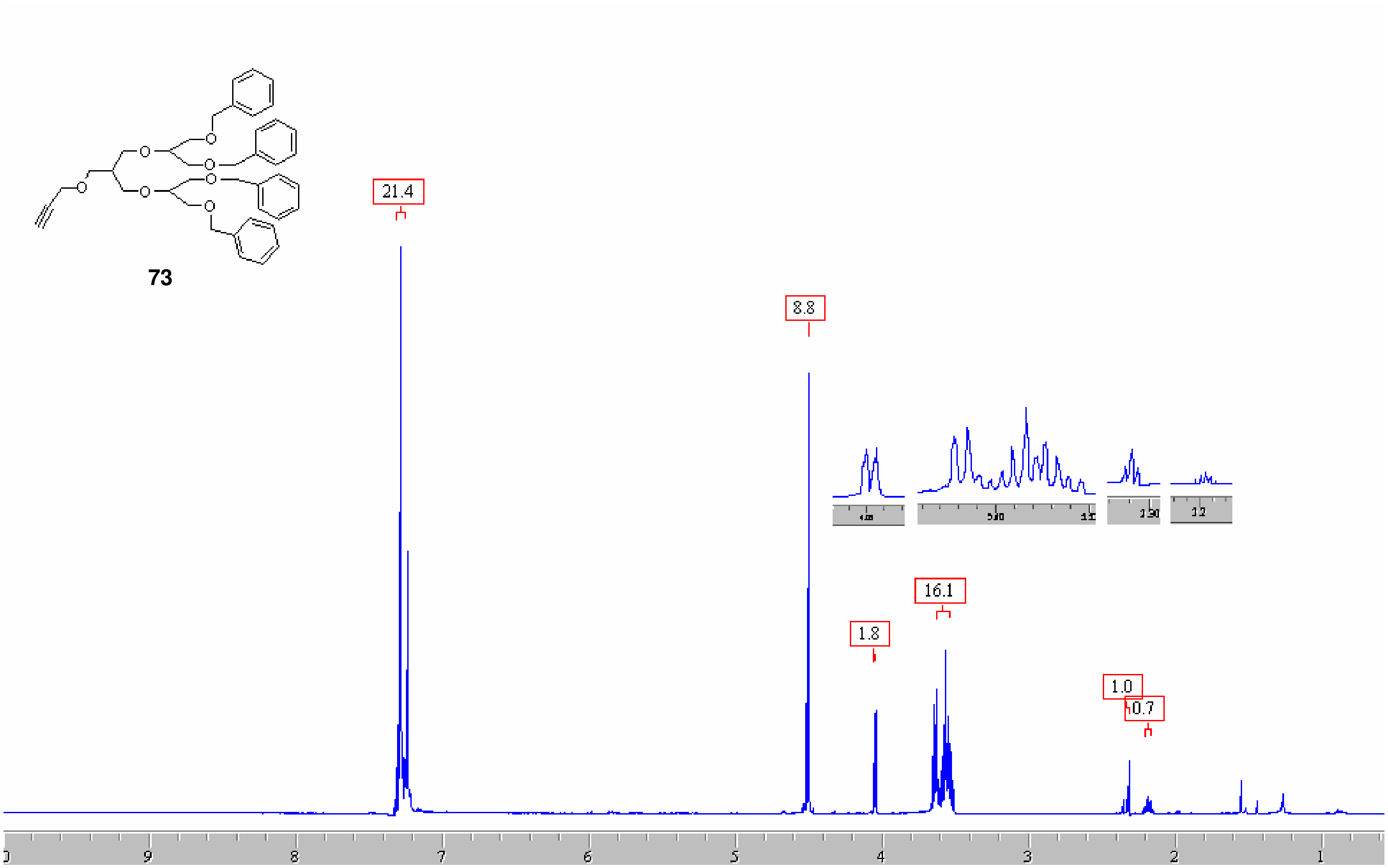


Figure A.25. ^{1}H NMR spectrum of G$_2$-acetylene **73**

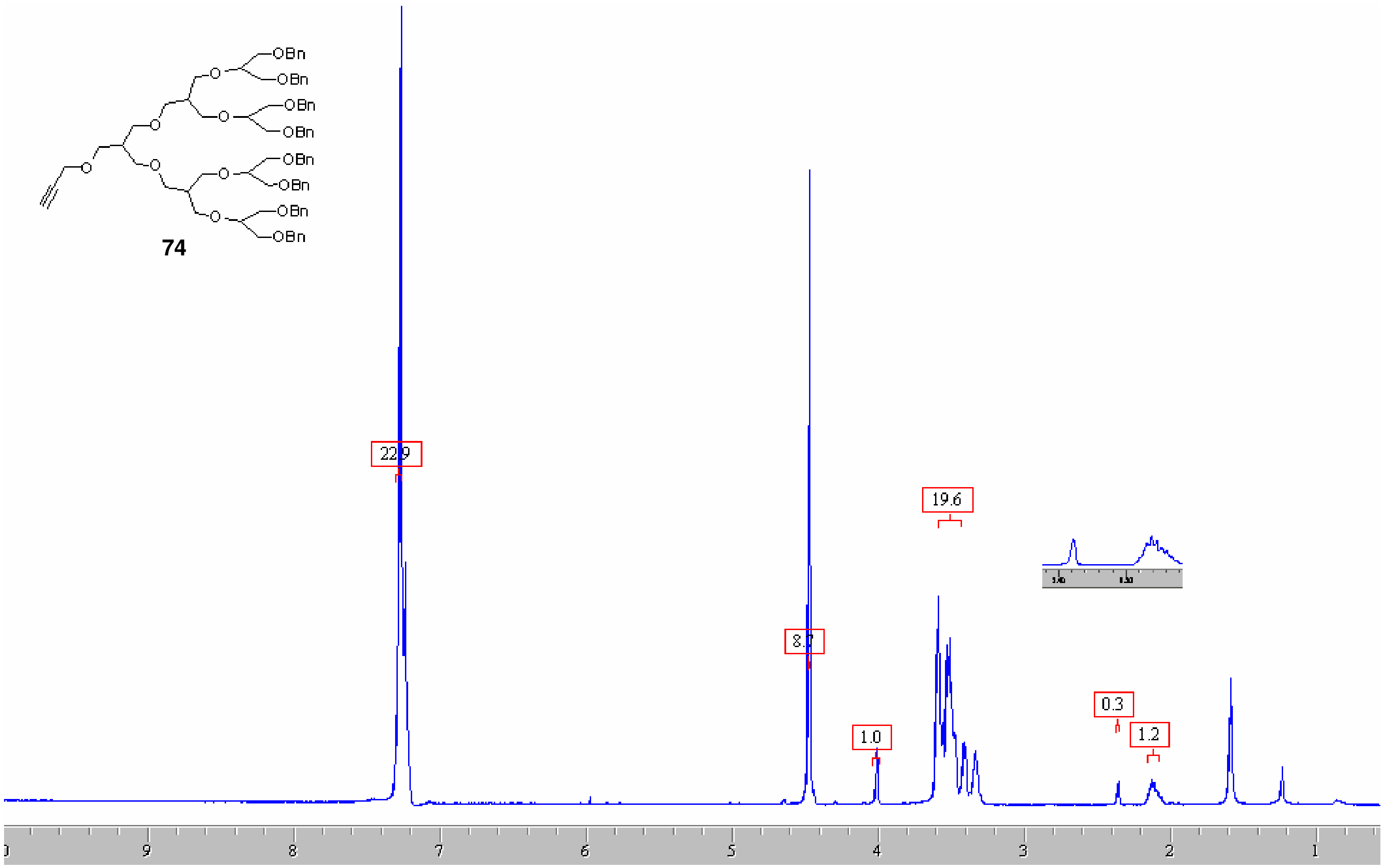


Figure A.26. ^{1}H NMR spectrum of G$_3$-acetylene **74**

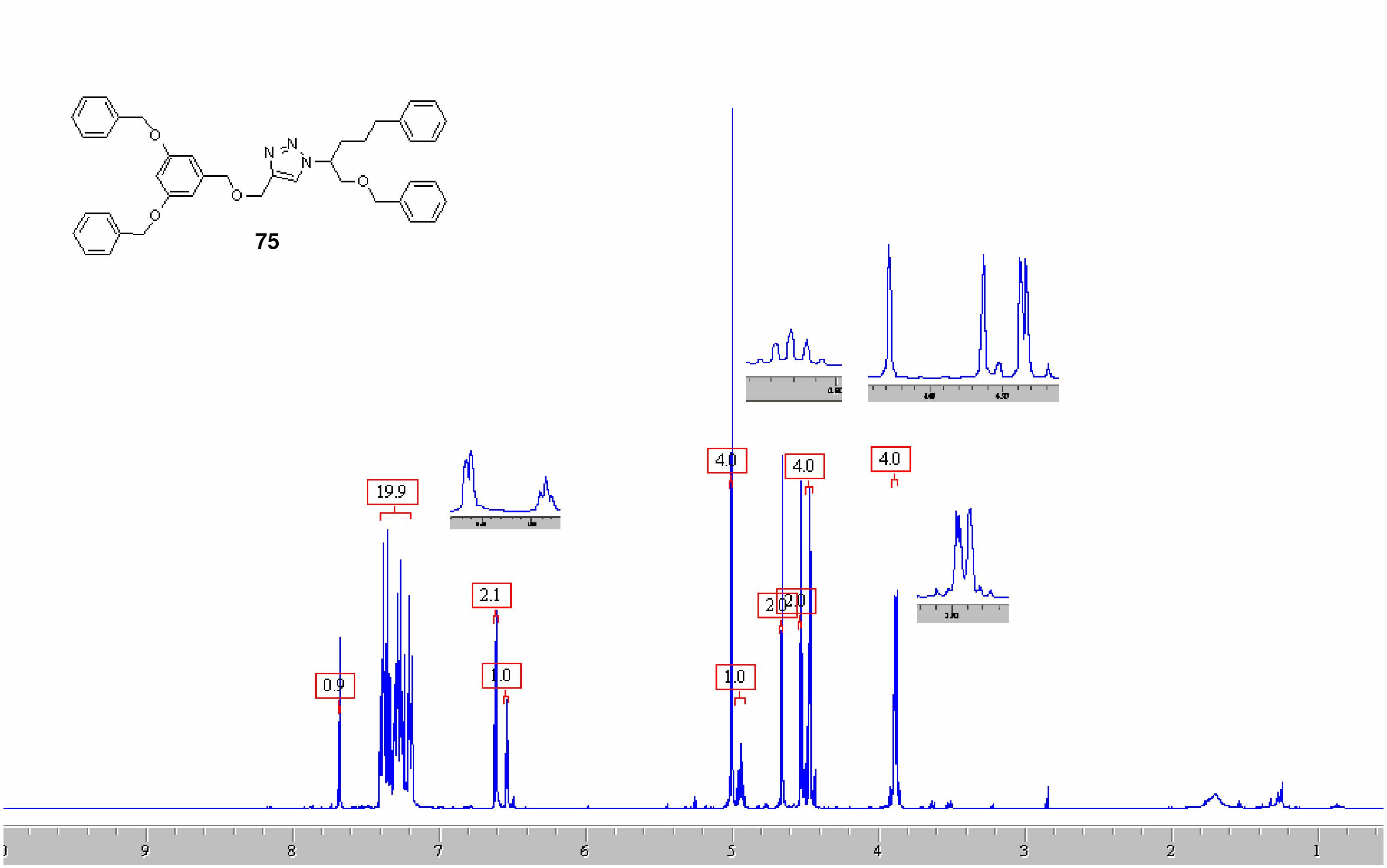


Figure A.27. ^{1}H NMR spectrum of A_1-B_1 **75**

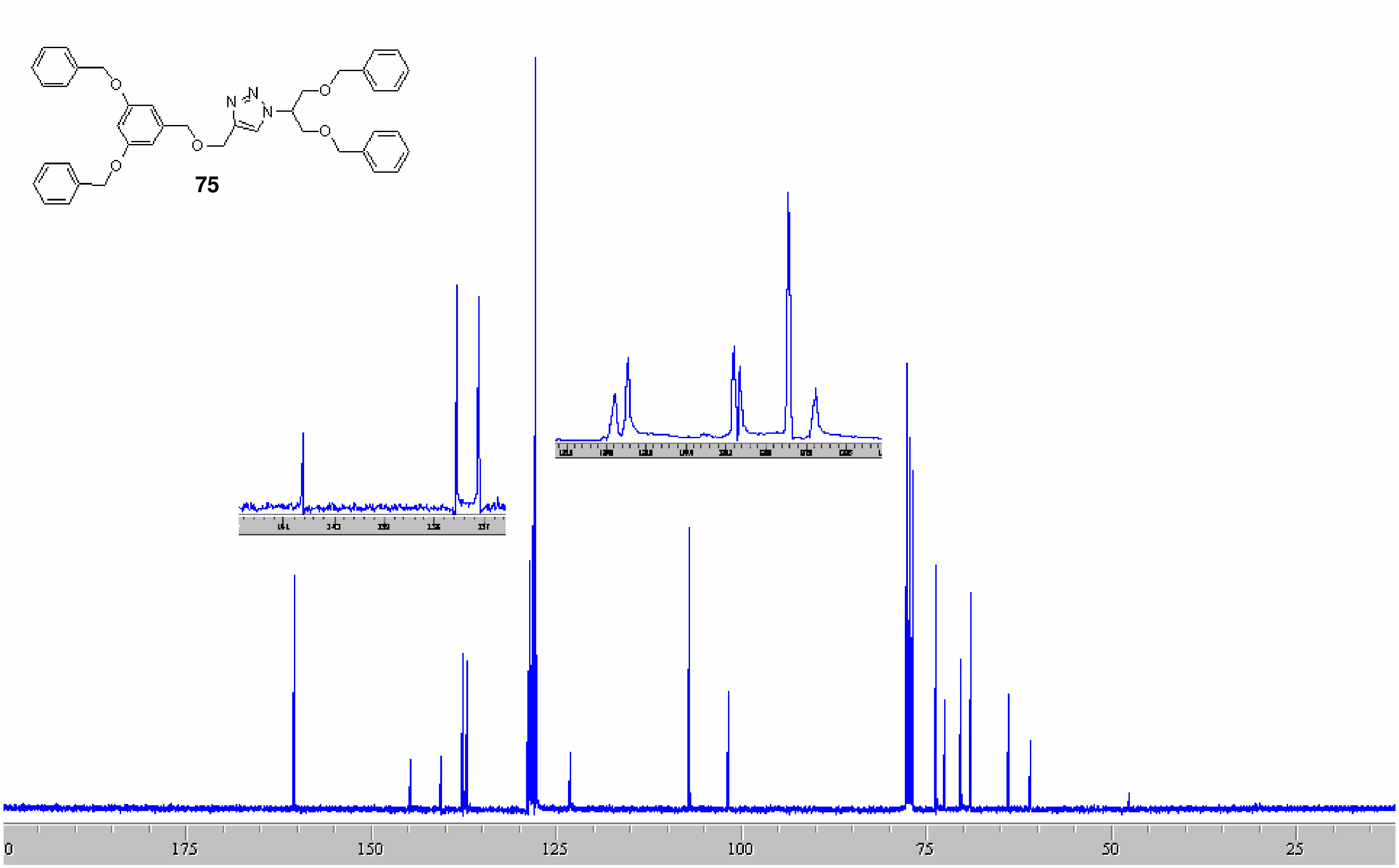


Figure A.28. ^{13}C NMR spectrum of A$_1$-B$_1$ **75**

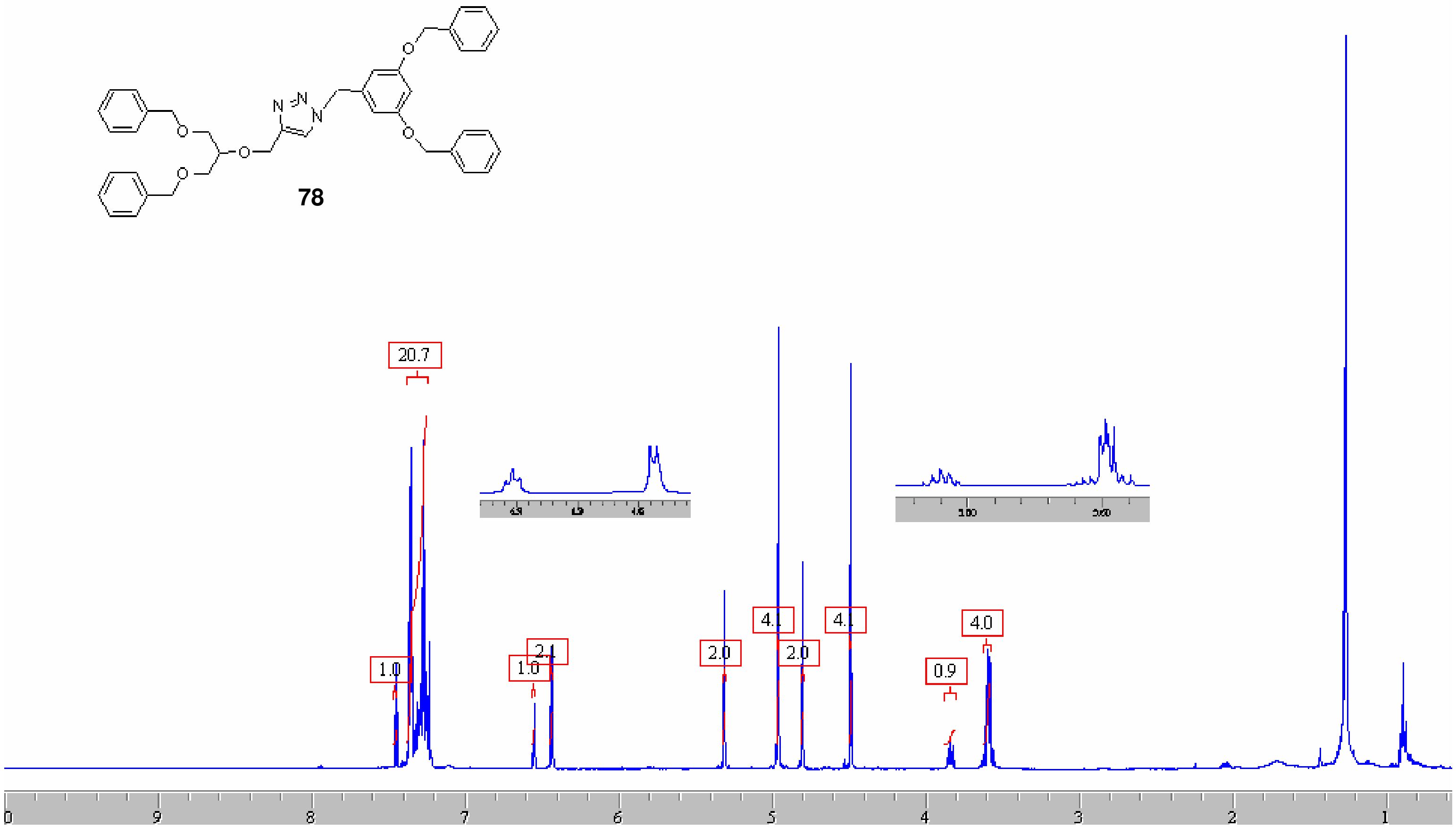


Figure A.29. ^{1}H NMR spectrum of B$_1$-A$_1$ **78**

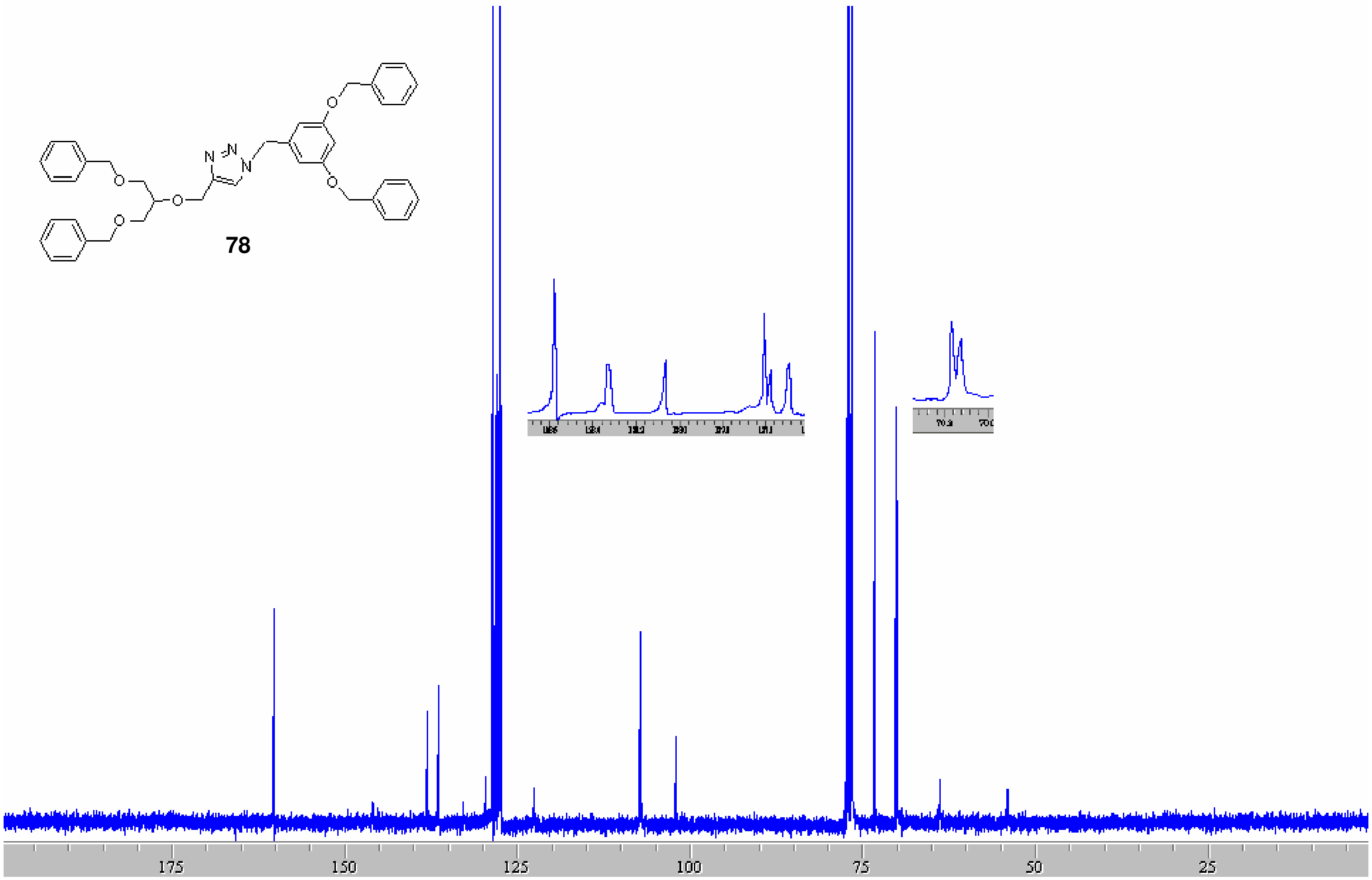


Figure A.30. ^{13}C NMR spectrum of B$_1$-A$_1$ **78**

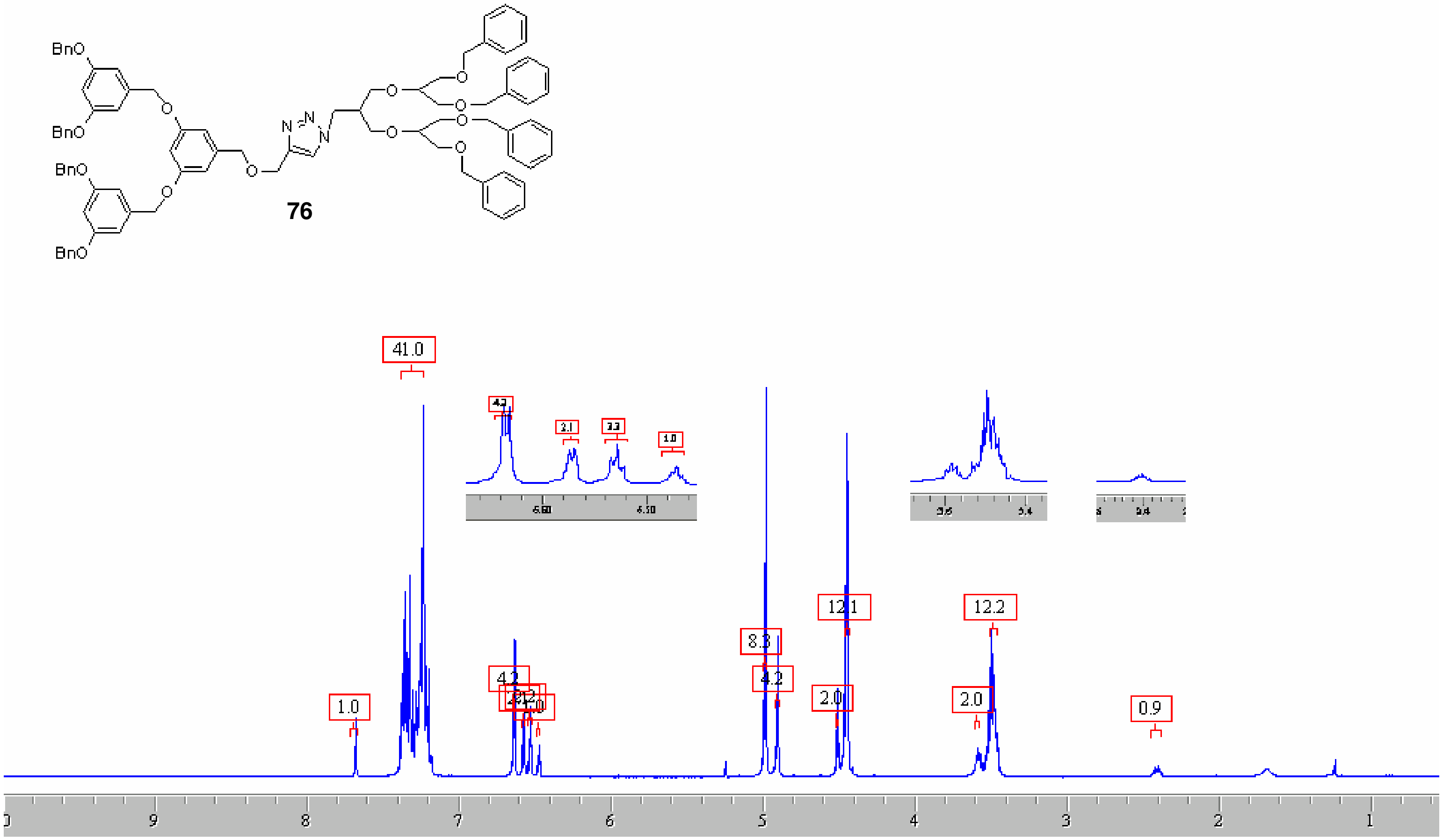


Figure A.31. ^{1}H NMR spectrum of A_2-B_2 **76**

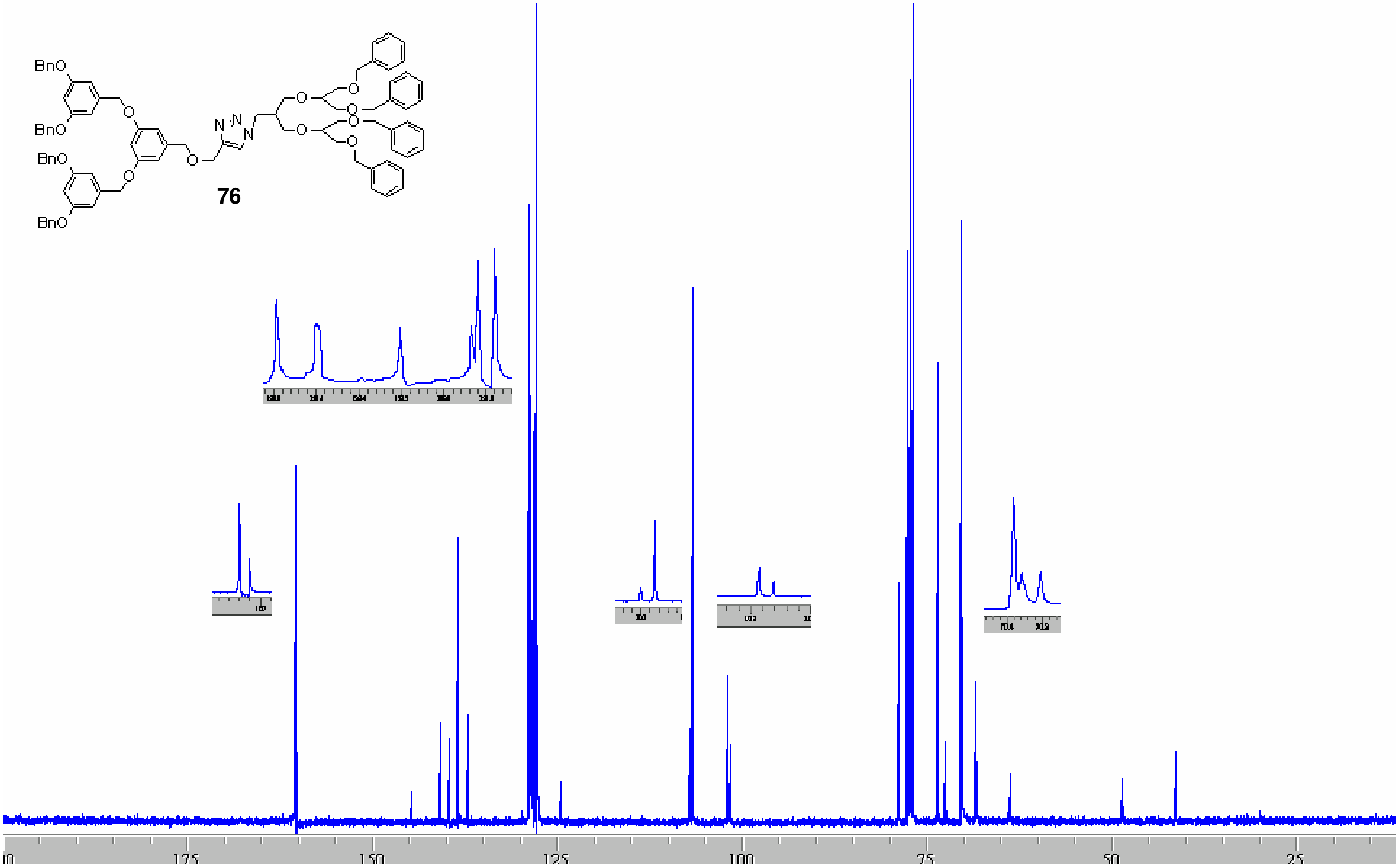


Figure A.32. ^{13}C NMR spectrum of A_2-B_2 **76**

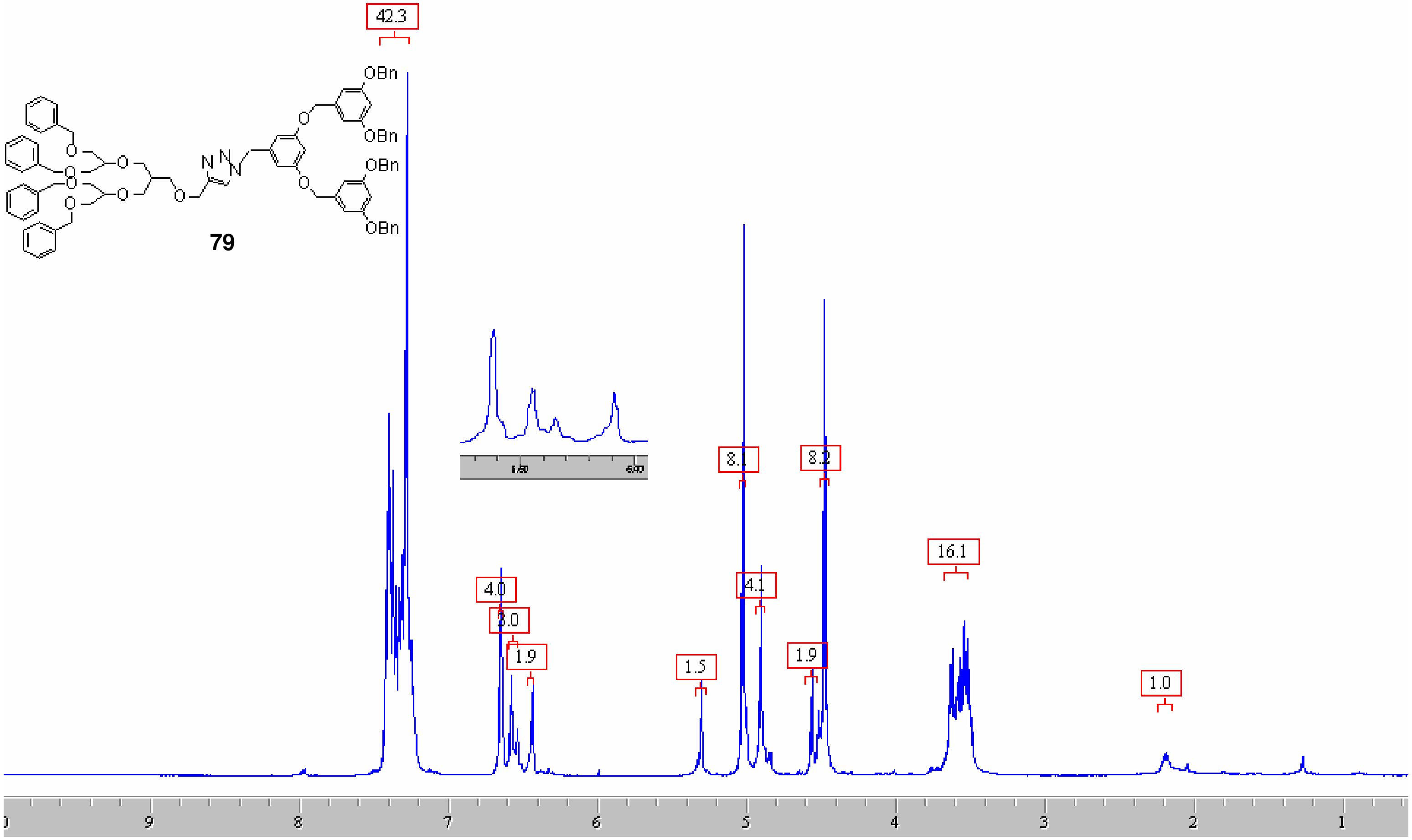


Figure A.33. ^{1}H NMR spectrum of B_2-A_2 **79**

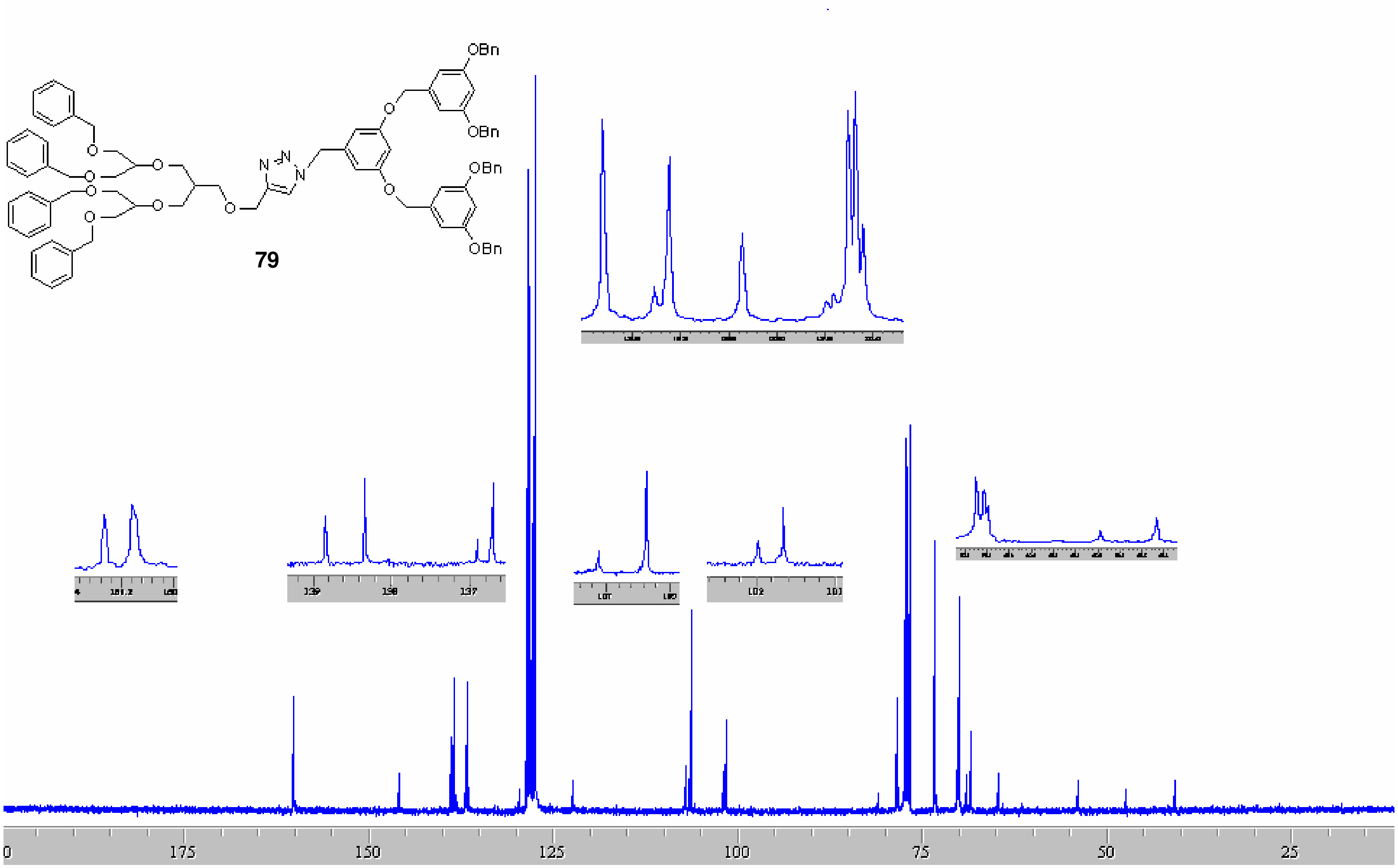


Figure A.34. ^{13}C NMR spectrum of B_2-A_2 **79**

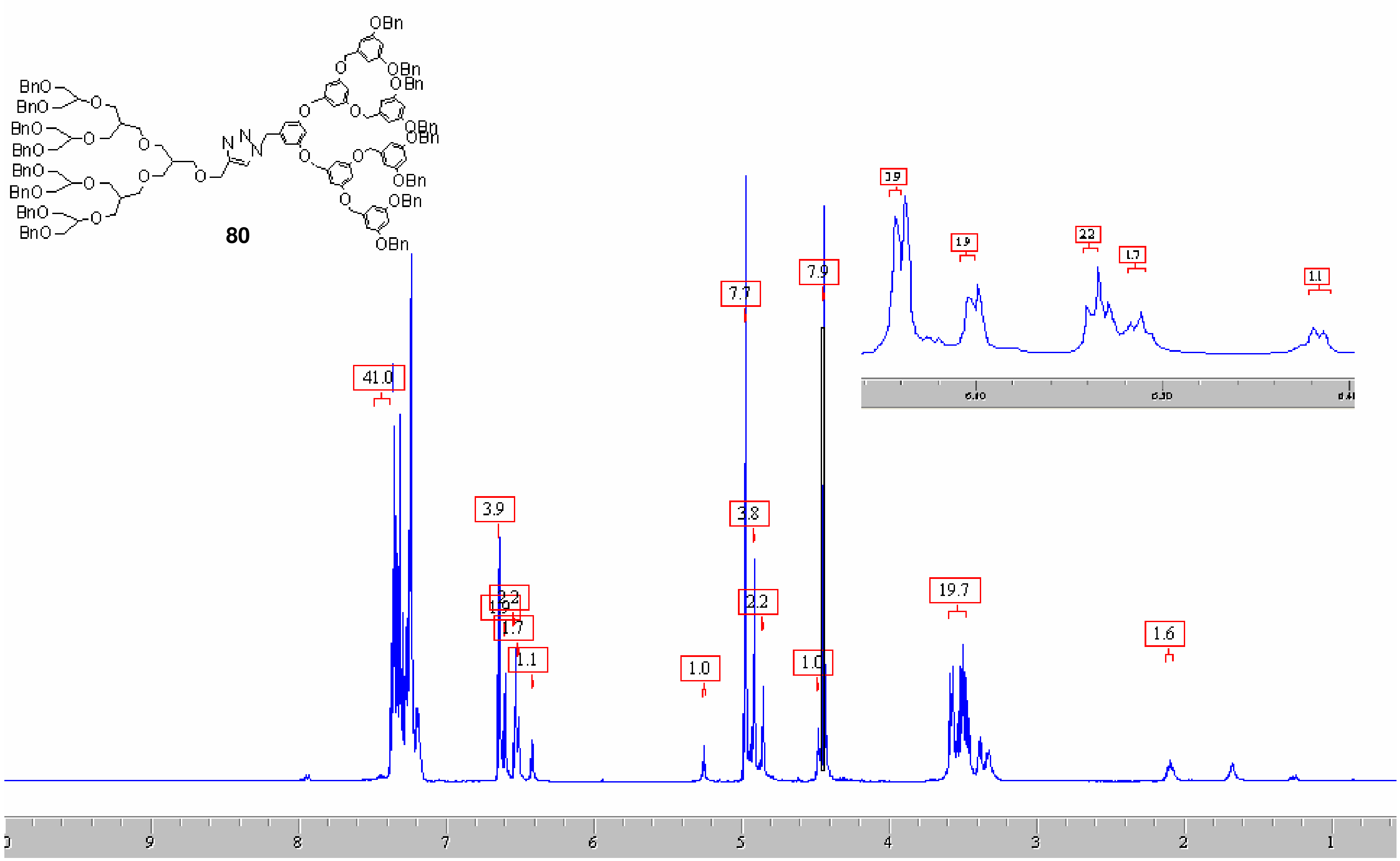


Figure A.35. ^{1}H NMR spectrum of B$_3$-A$_3$ **80**

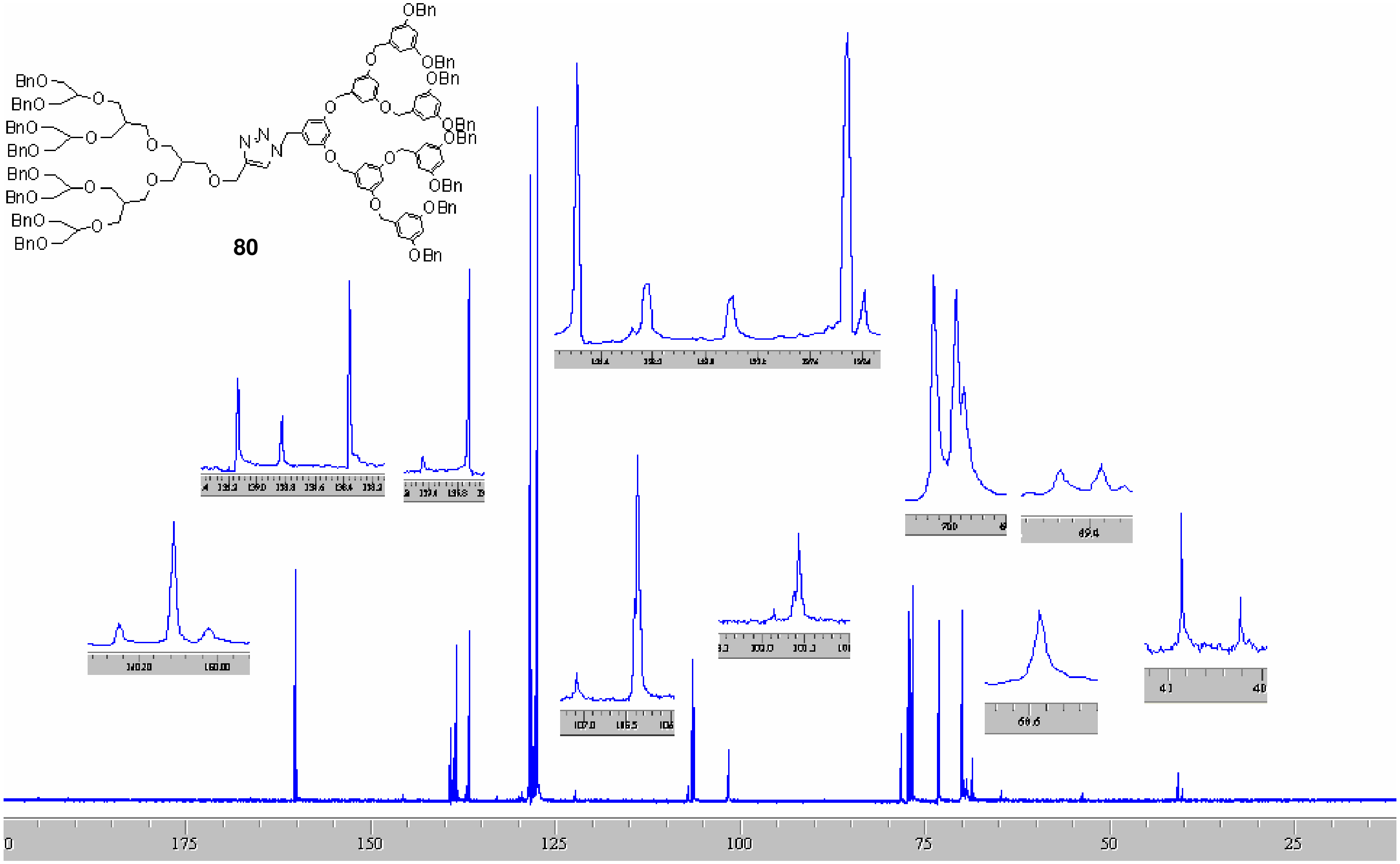
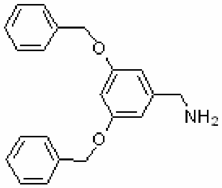


Figure A.36. ^{13}C NMR spectrum of B_3-A_3 **80**



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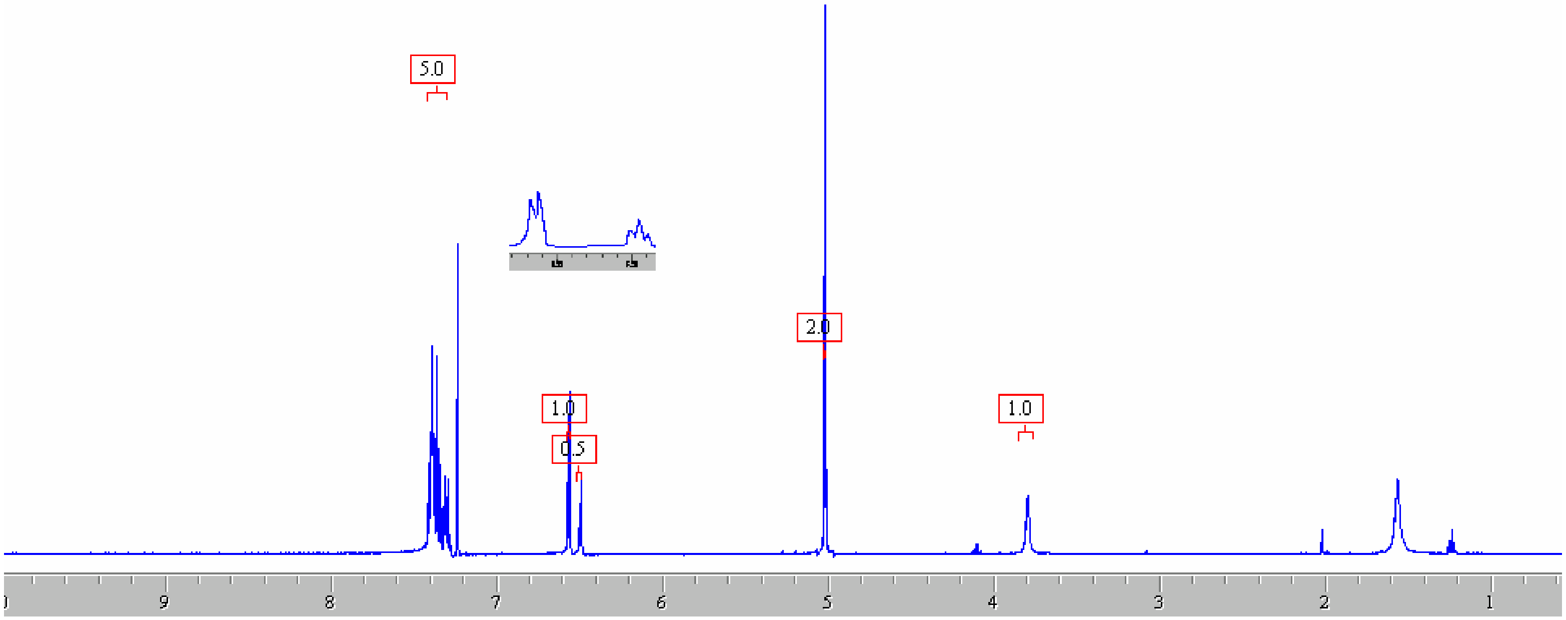


Figure A.37. ^{1}H NMR spectrum of G$_1$-amine **104**

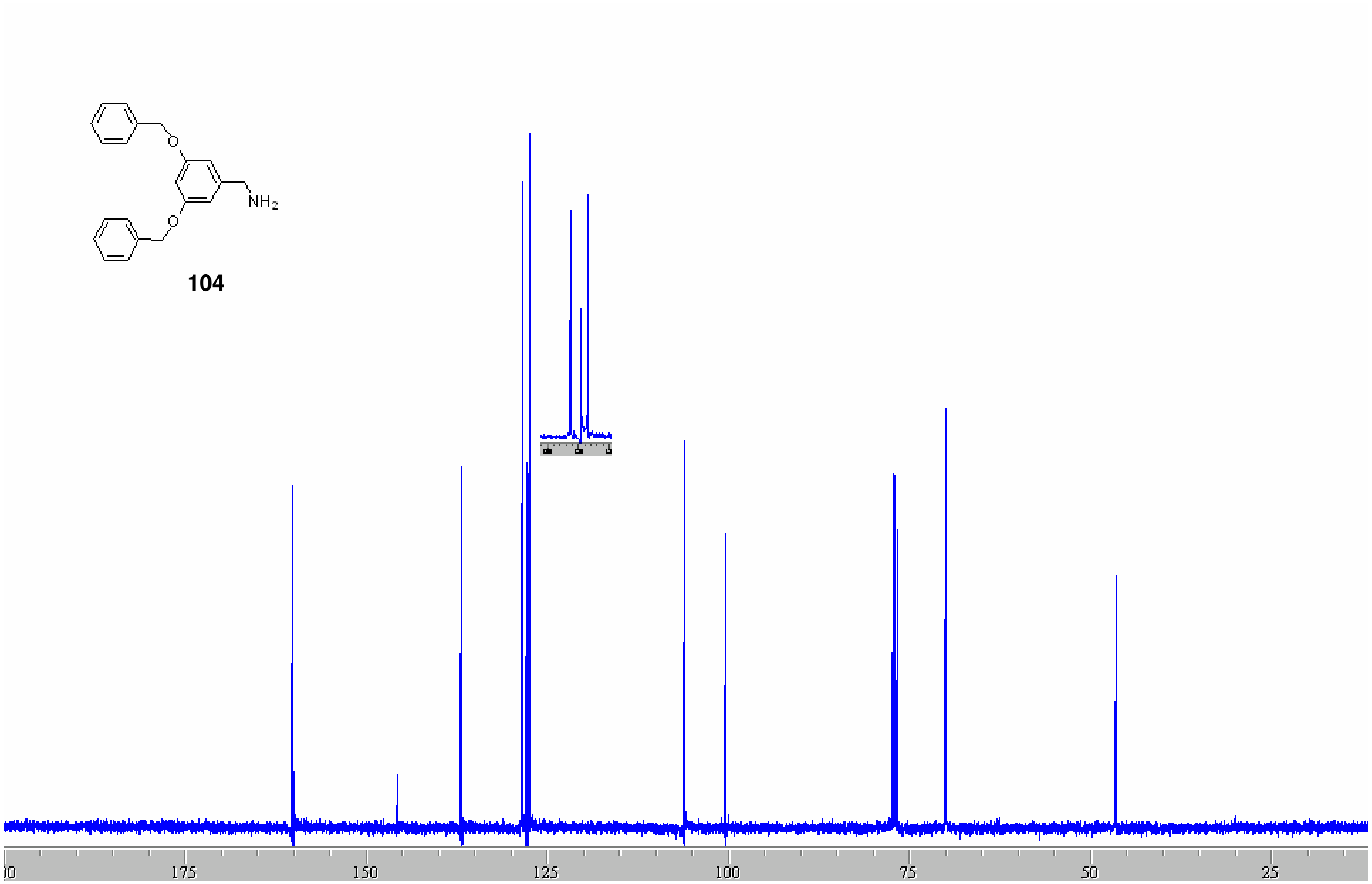


Figure A.38. ^{13}C NMR spectrum of G$_1$-amine **104**

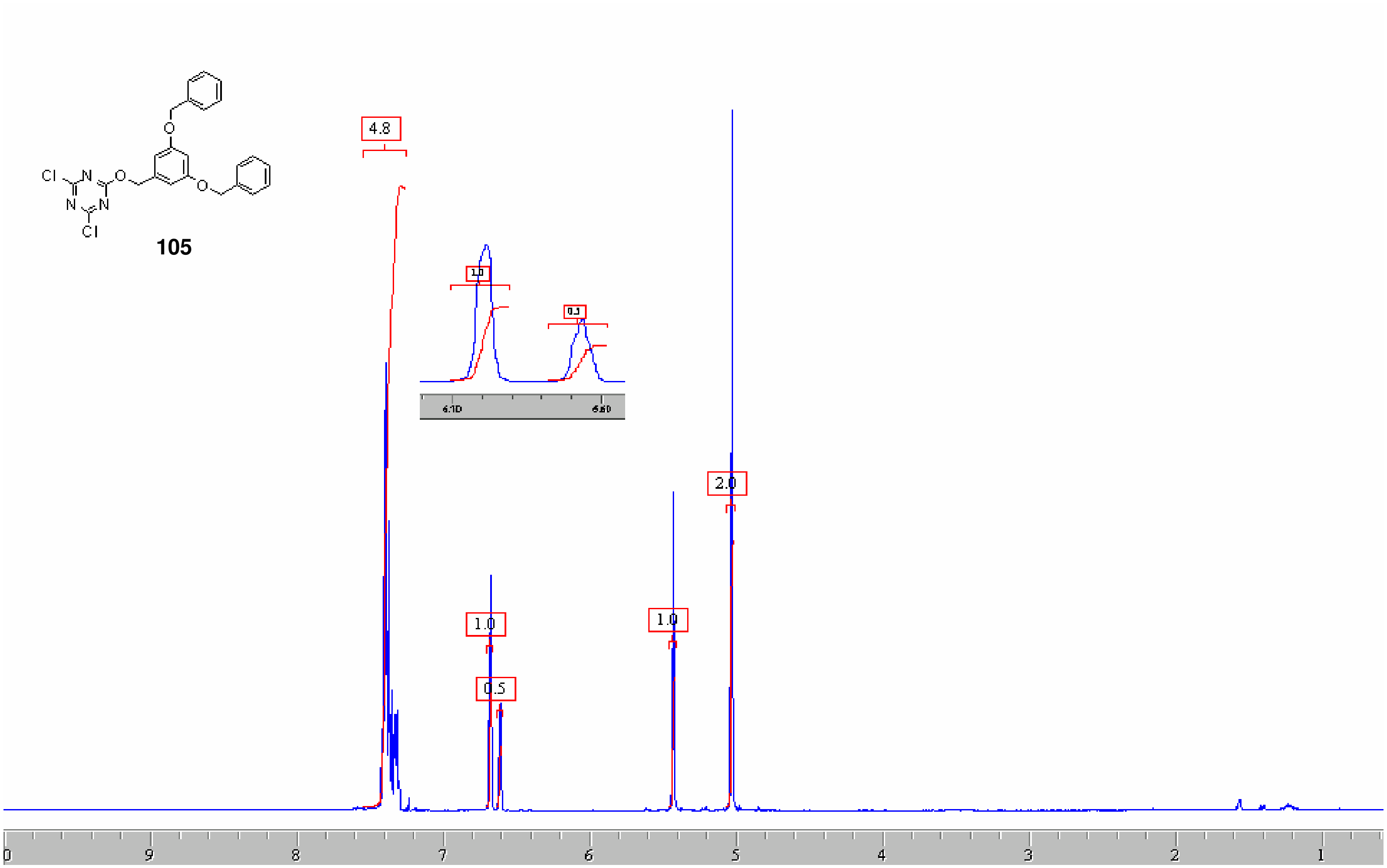


Figure A.39. ^{1}H NMR spectrum of G$_1$-alcohol substituted cyanuric chloride **105**

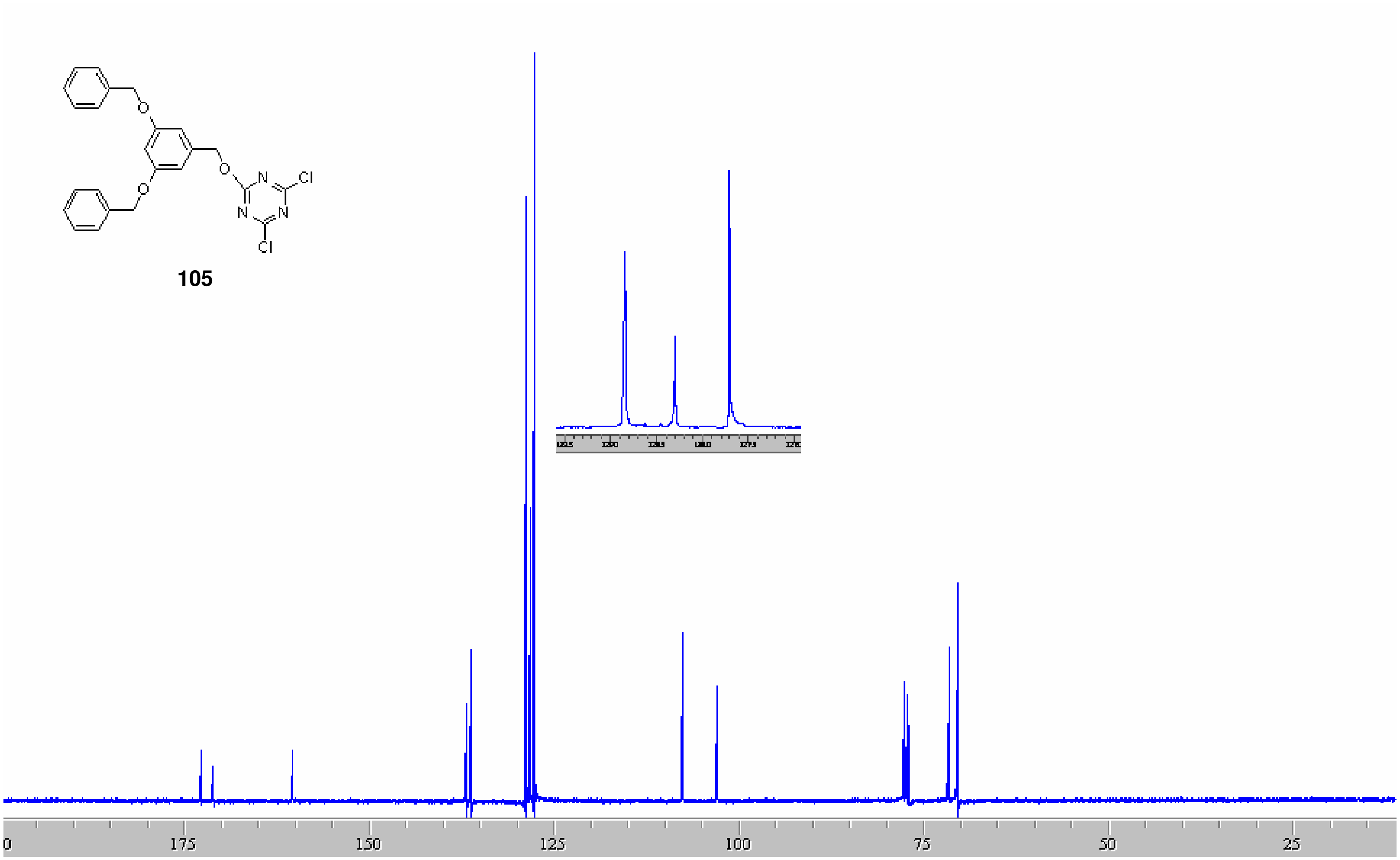


Figure A.40. ^{13}C NMR spectrum of G$_1$-alcohol substituted cyanuric chloride **105**

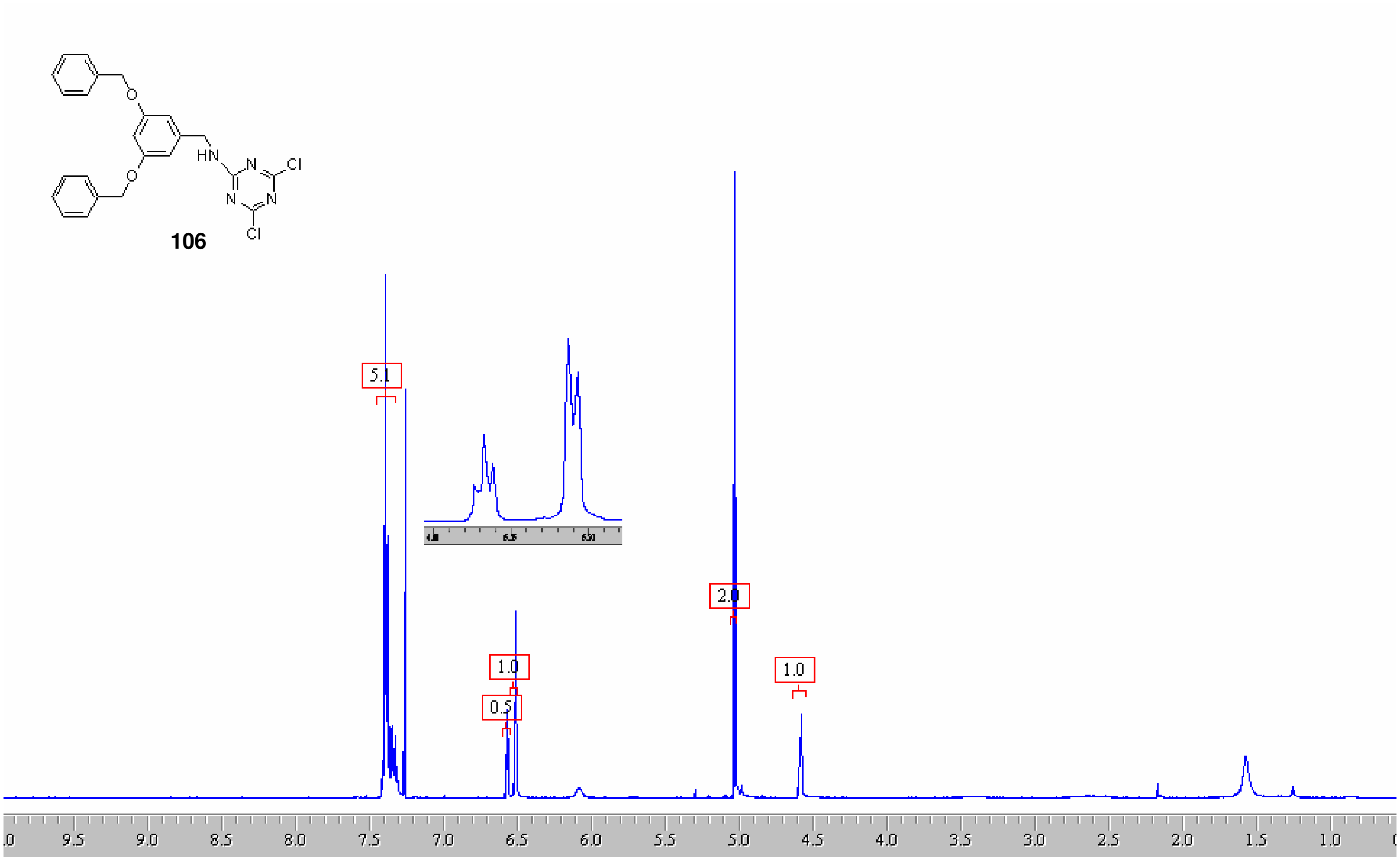
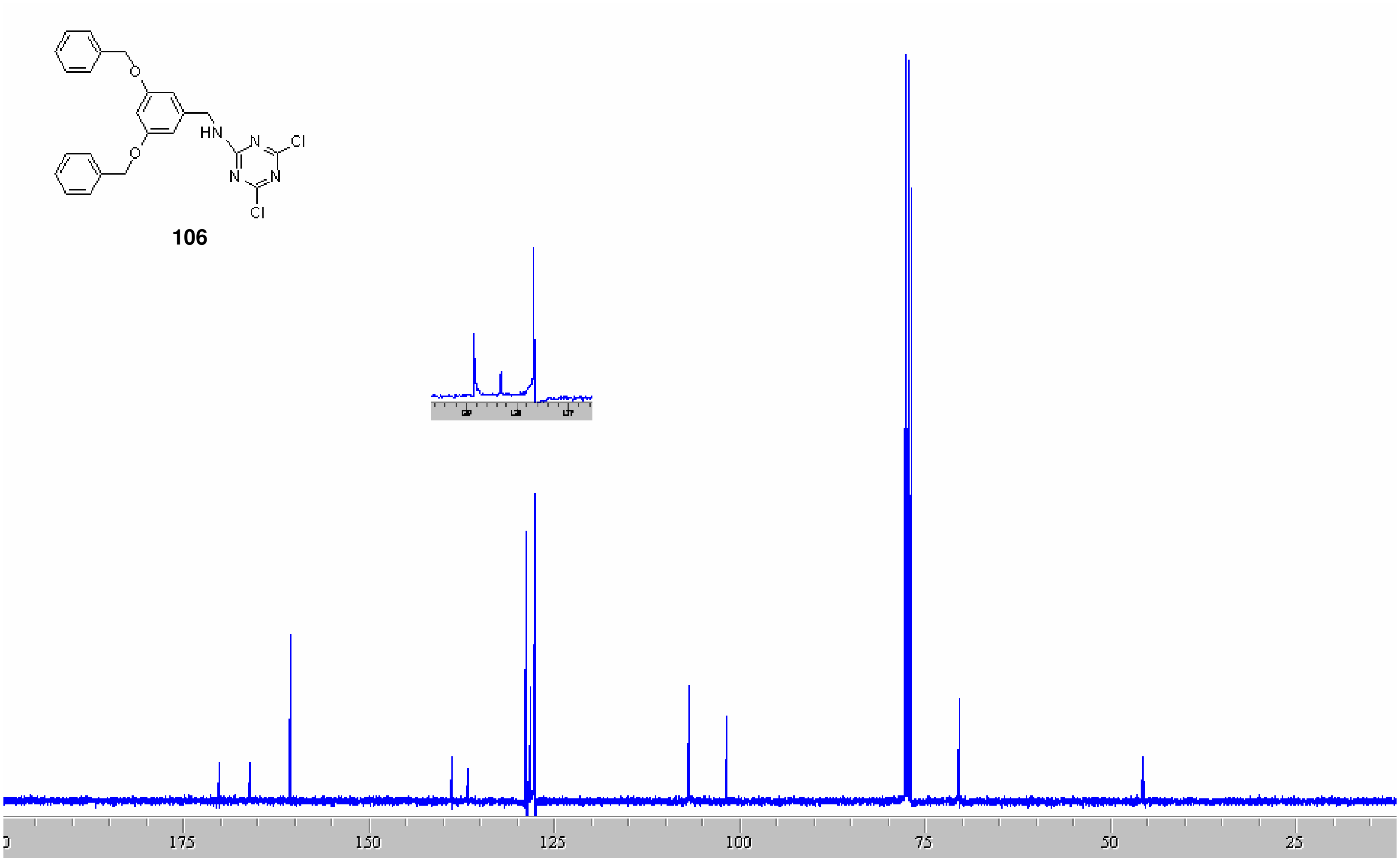


Figure A.41. ^{1}H NMR spectrum of G_1-amine substituted cyanuric chloride **106**



106

Figure A.42. ^{13}C NMR spectrum of G$_1$-amine substituted cyanuric chloride **106**

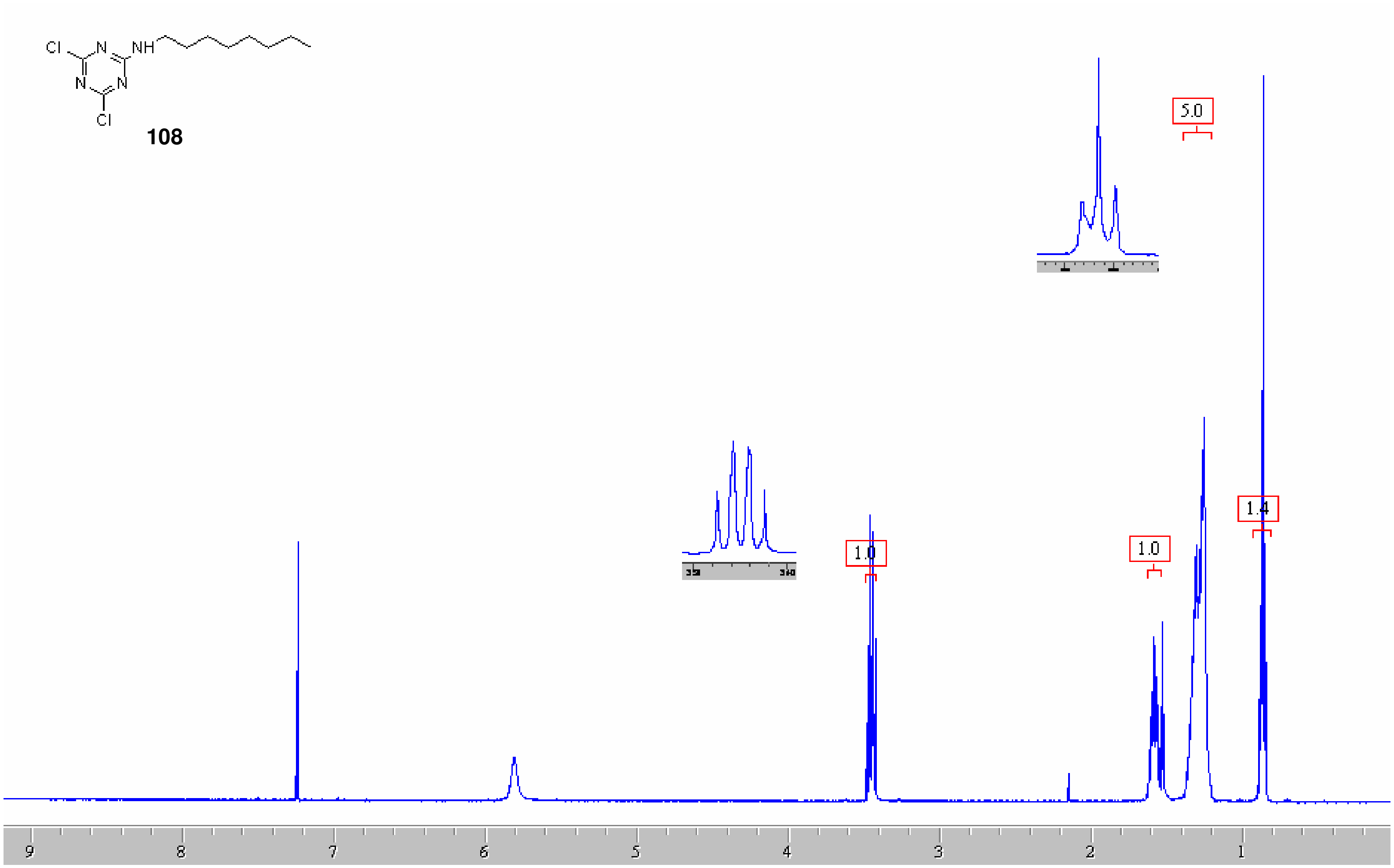
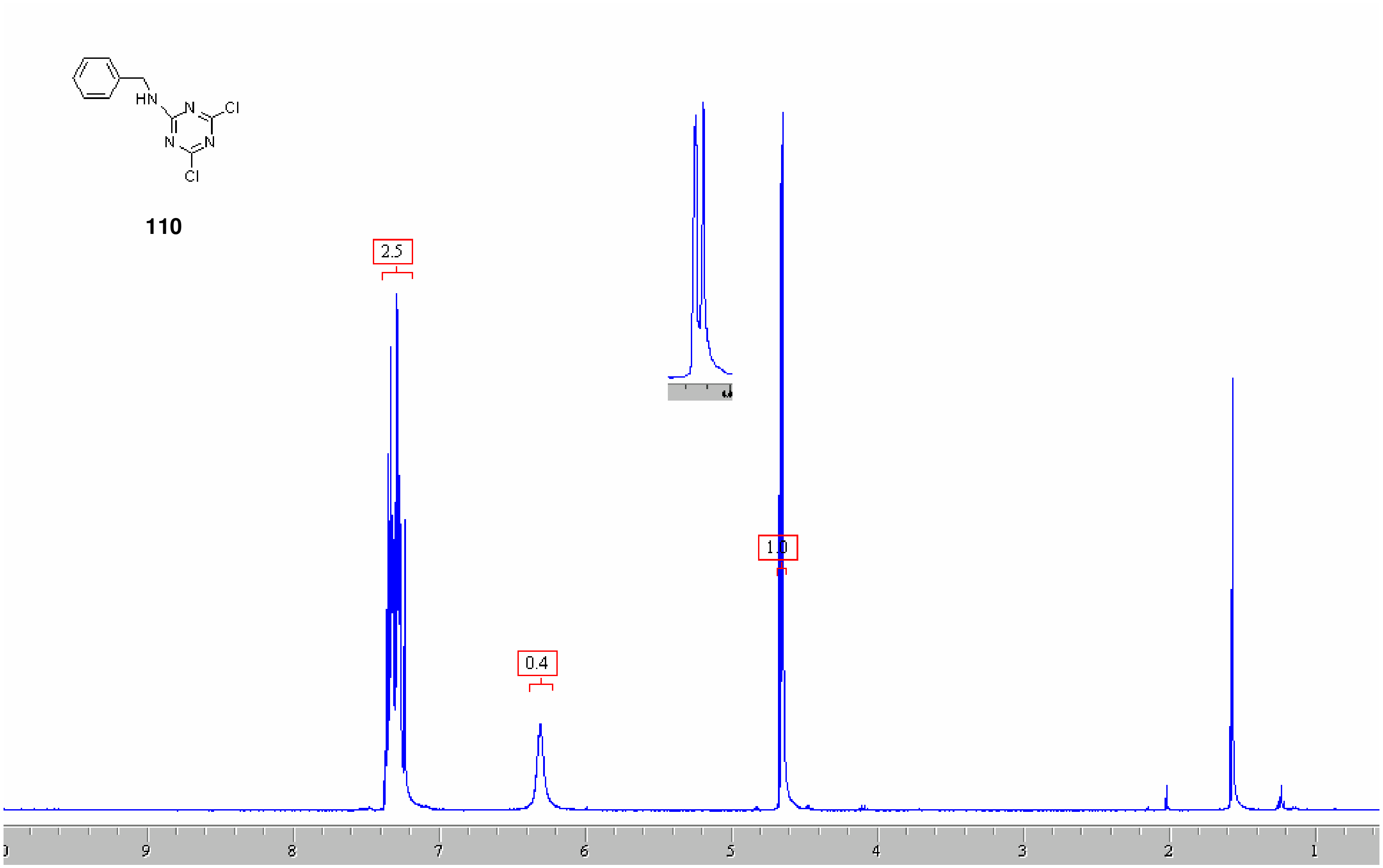


Figure A.43. ^{1}H NMR spectrum of octylamine substituted cyanuric chloride **108**



110

Figure A.44. ^{1}H NMR spectrum of benzylamine substituted cyanuric chloride **110**

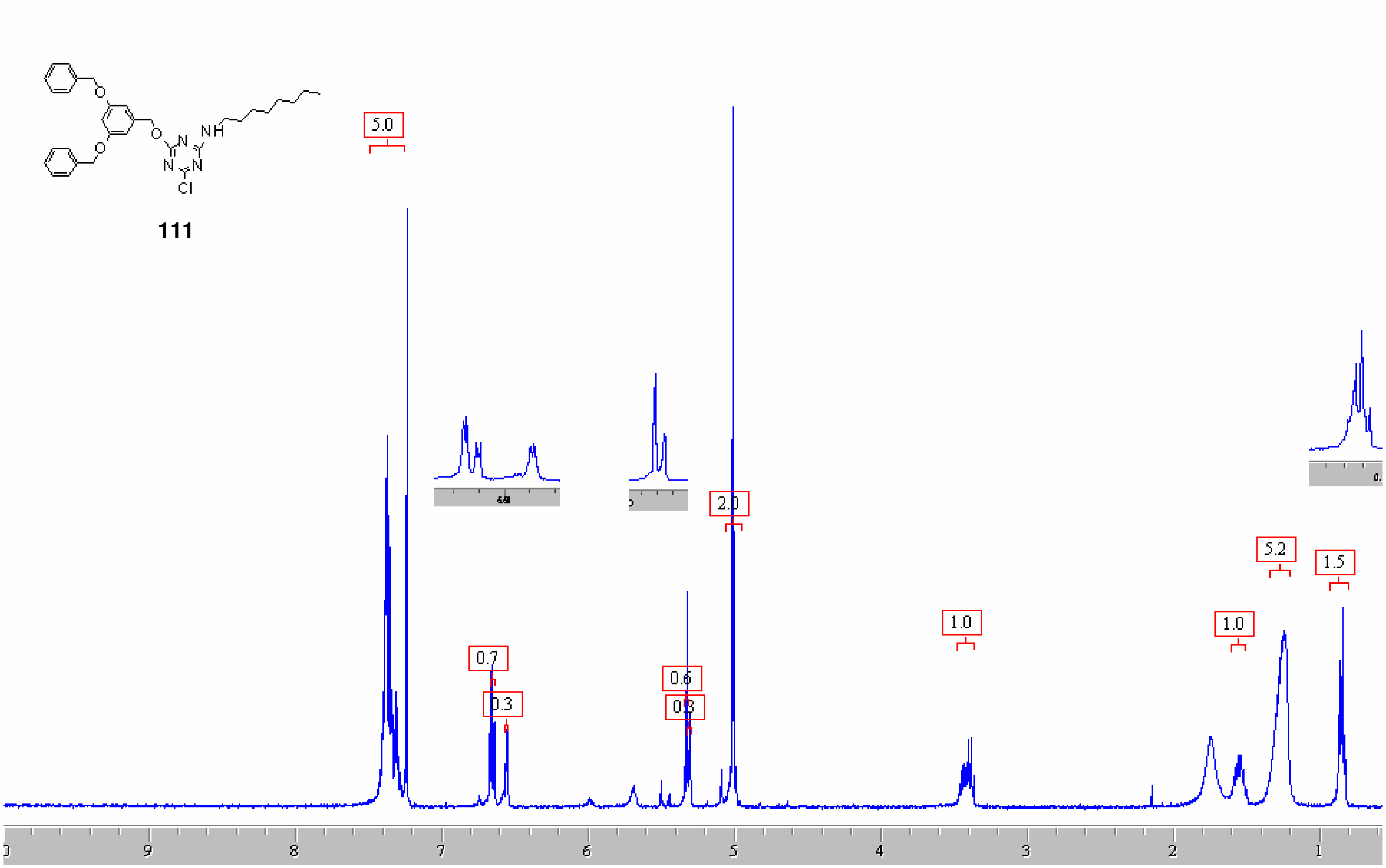


Figure A.45. ^{1}H NMR spectrum of disubstituted triazine **111**

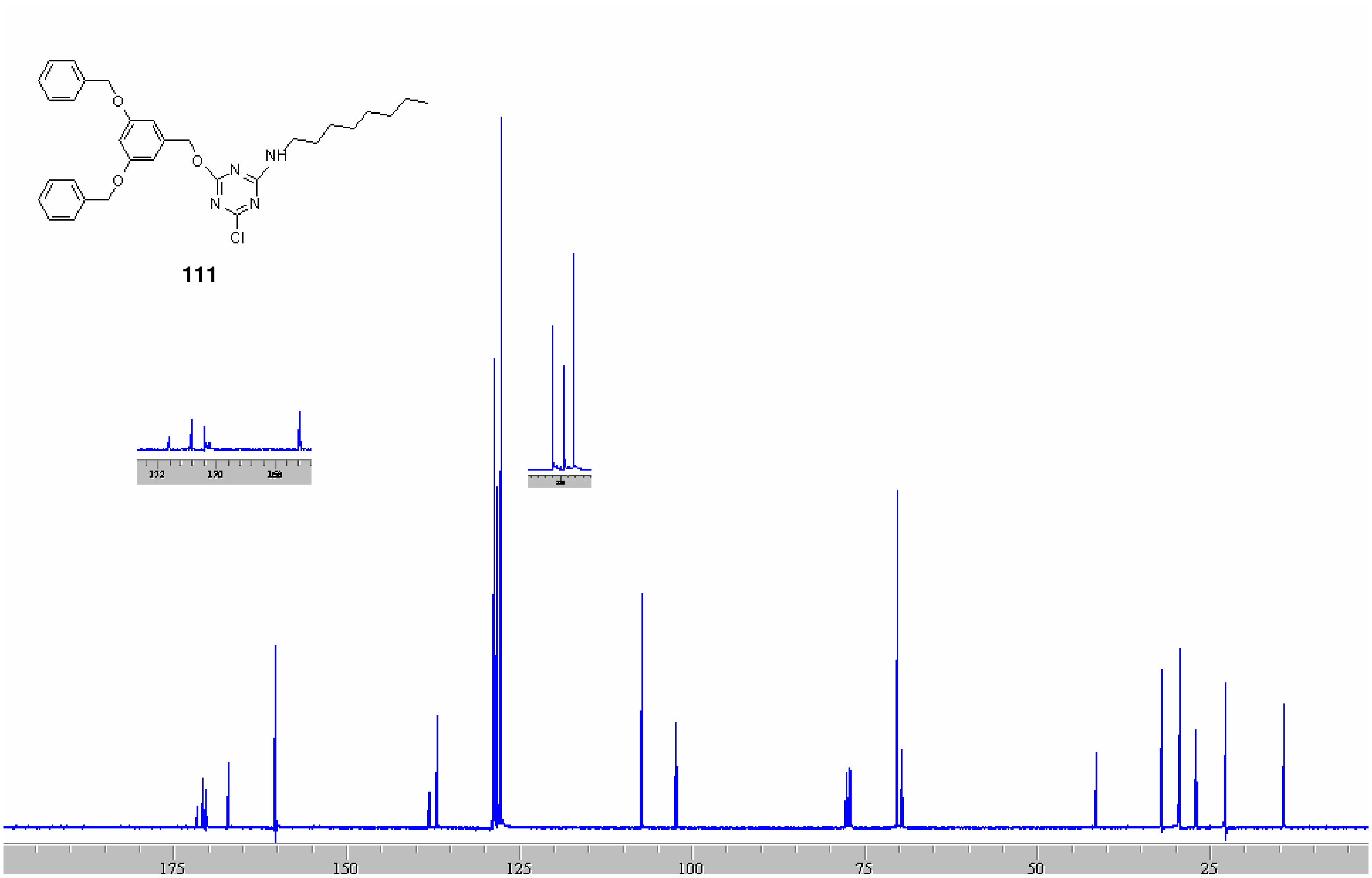


Figure A.46. ^{13}C NMR spectrum of disubstituted triazine **111**

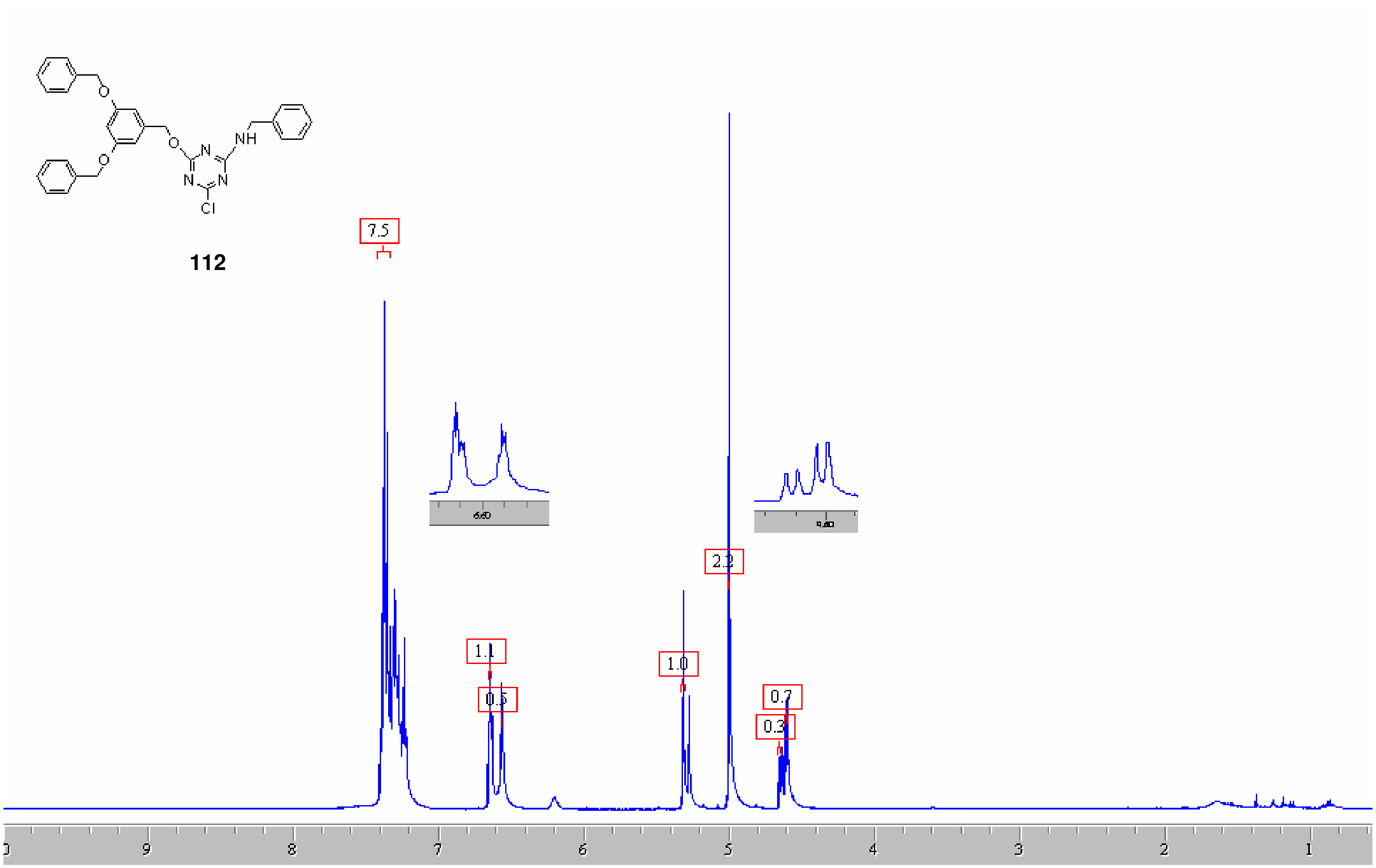
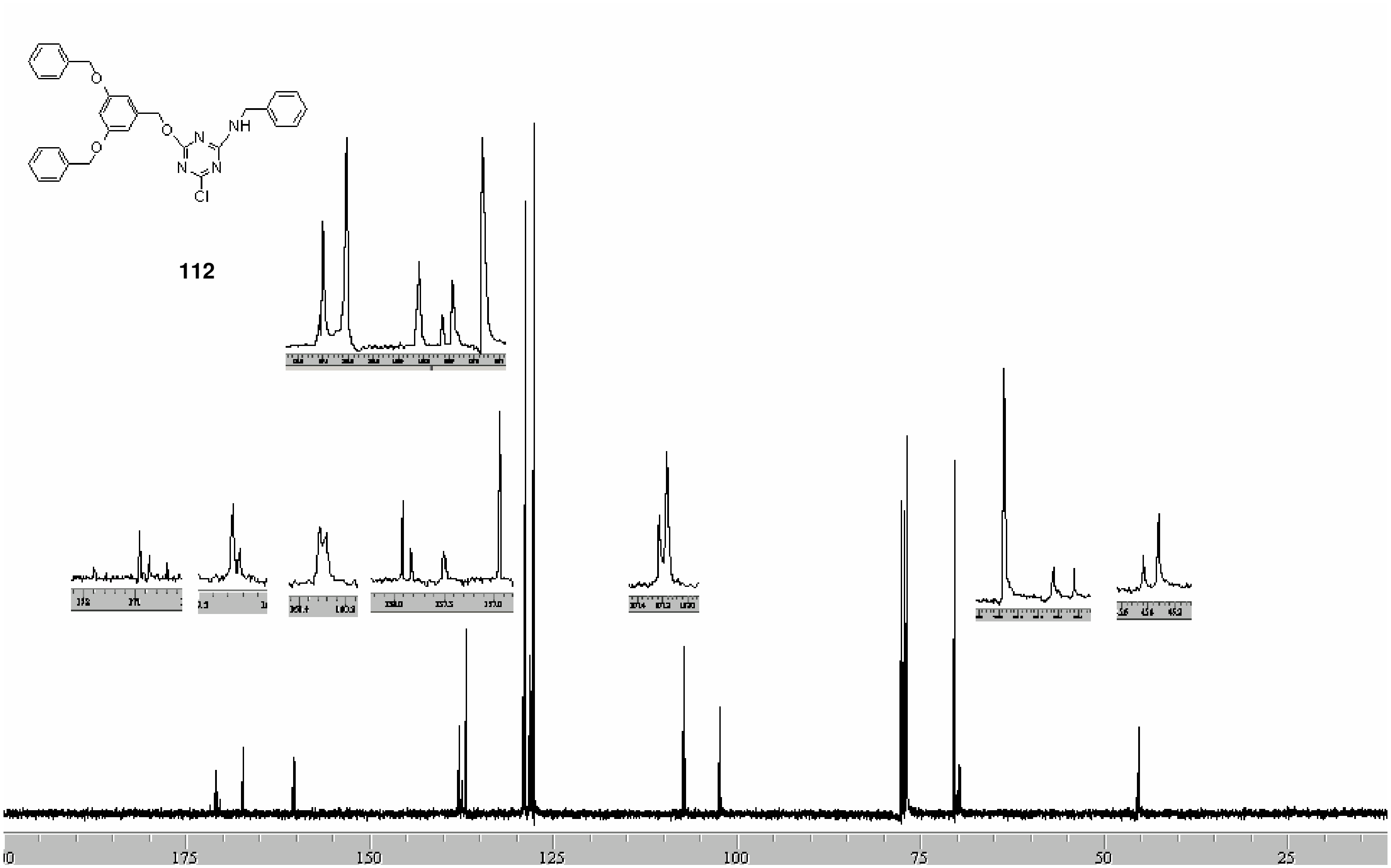


Figure A.47. ^{1}H NMR spectrum of disubstituted triazine **112**



112

Figure A.48. ^{13}C NMR spectrum of disubstituted triazine **112**

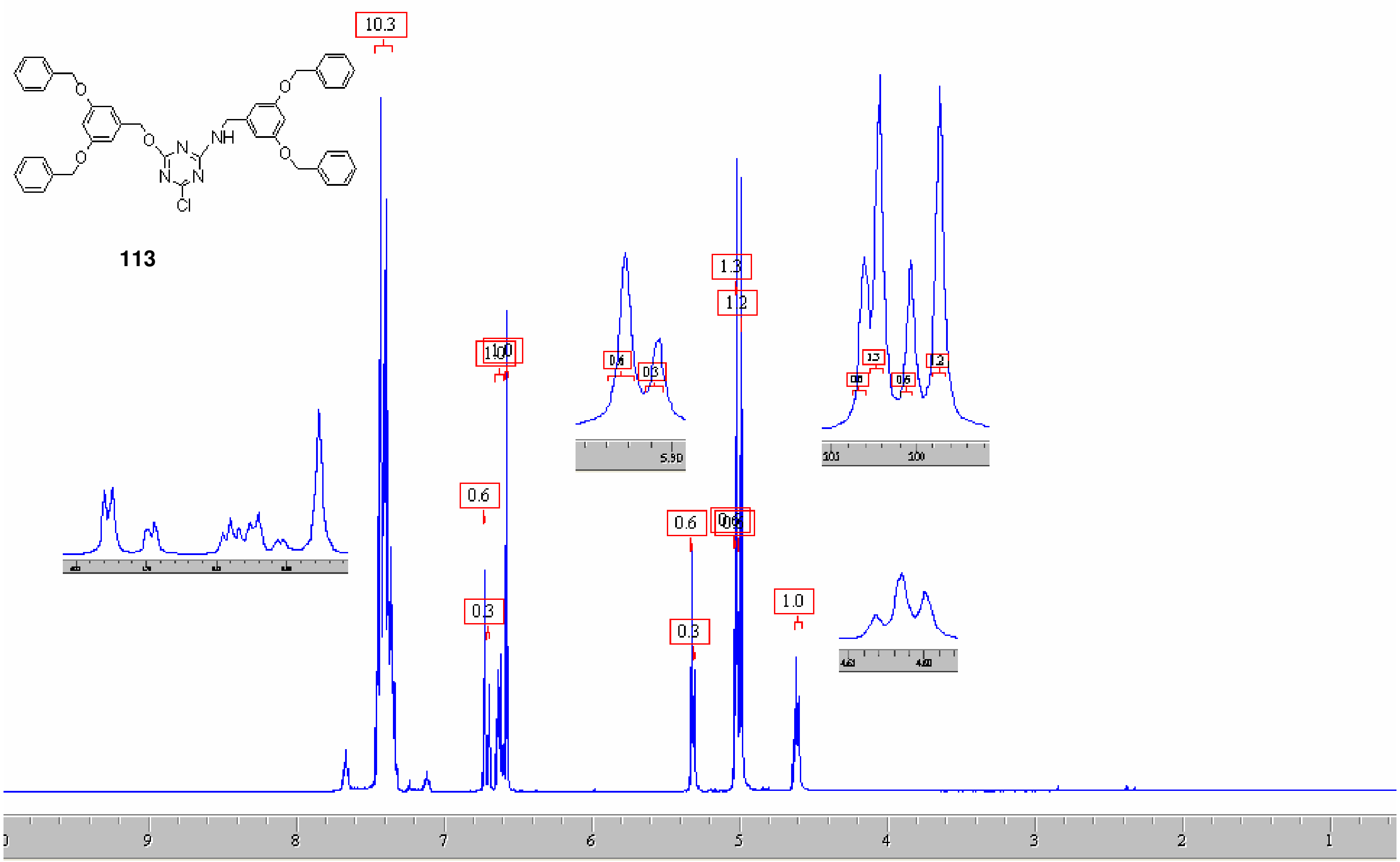


Figure A.49. ^{1}H NMR spectrum of disubstituted triazine **113**

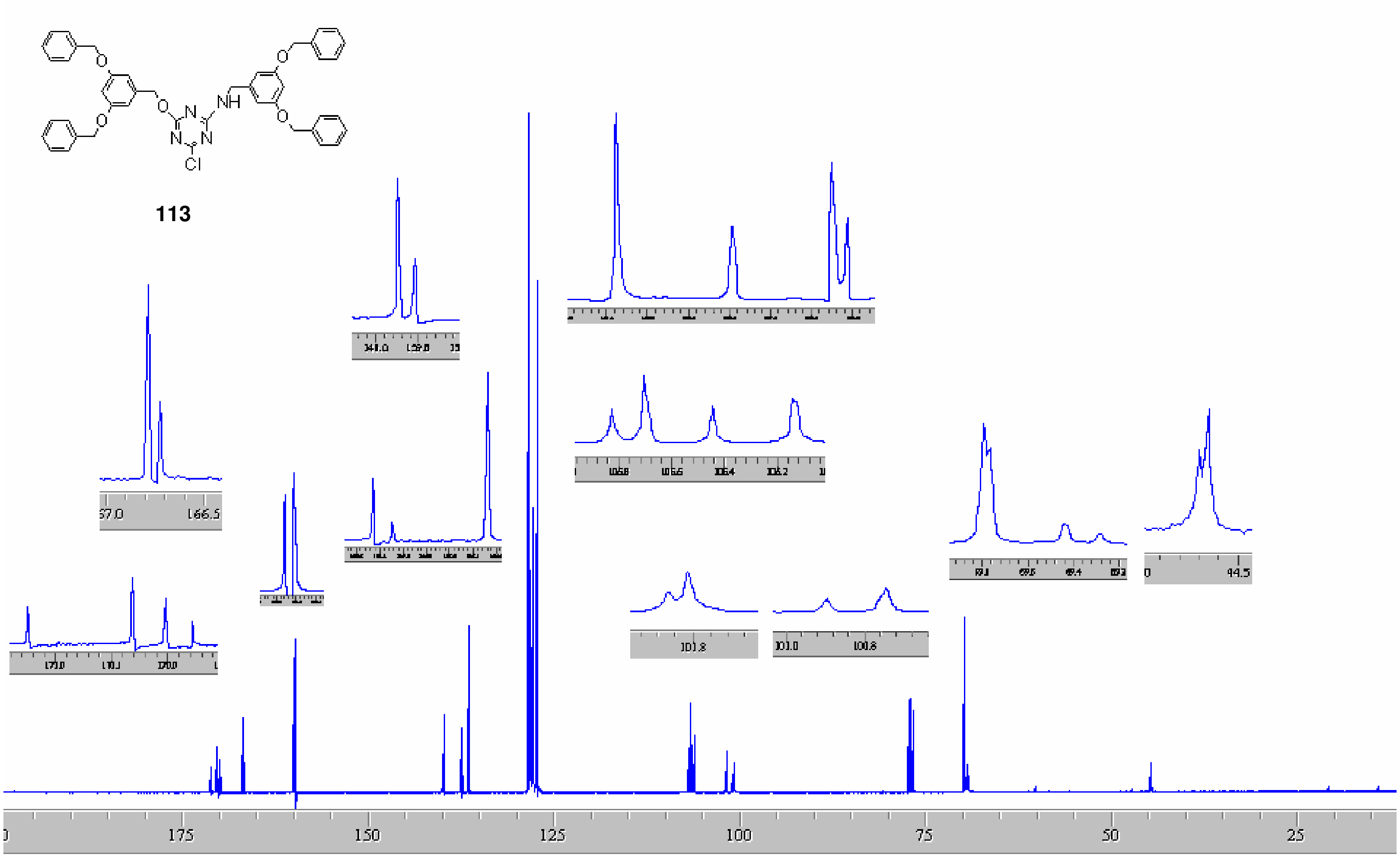


Figure A.50. ^{13}C NMR spectrum of disubstituted triazine **113**

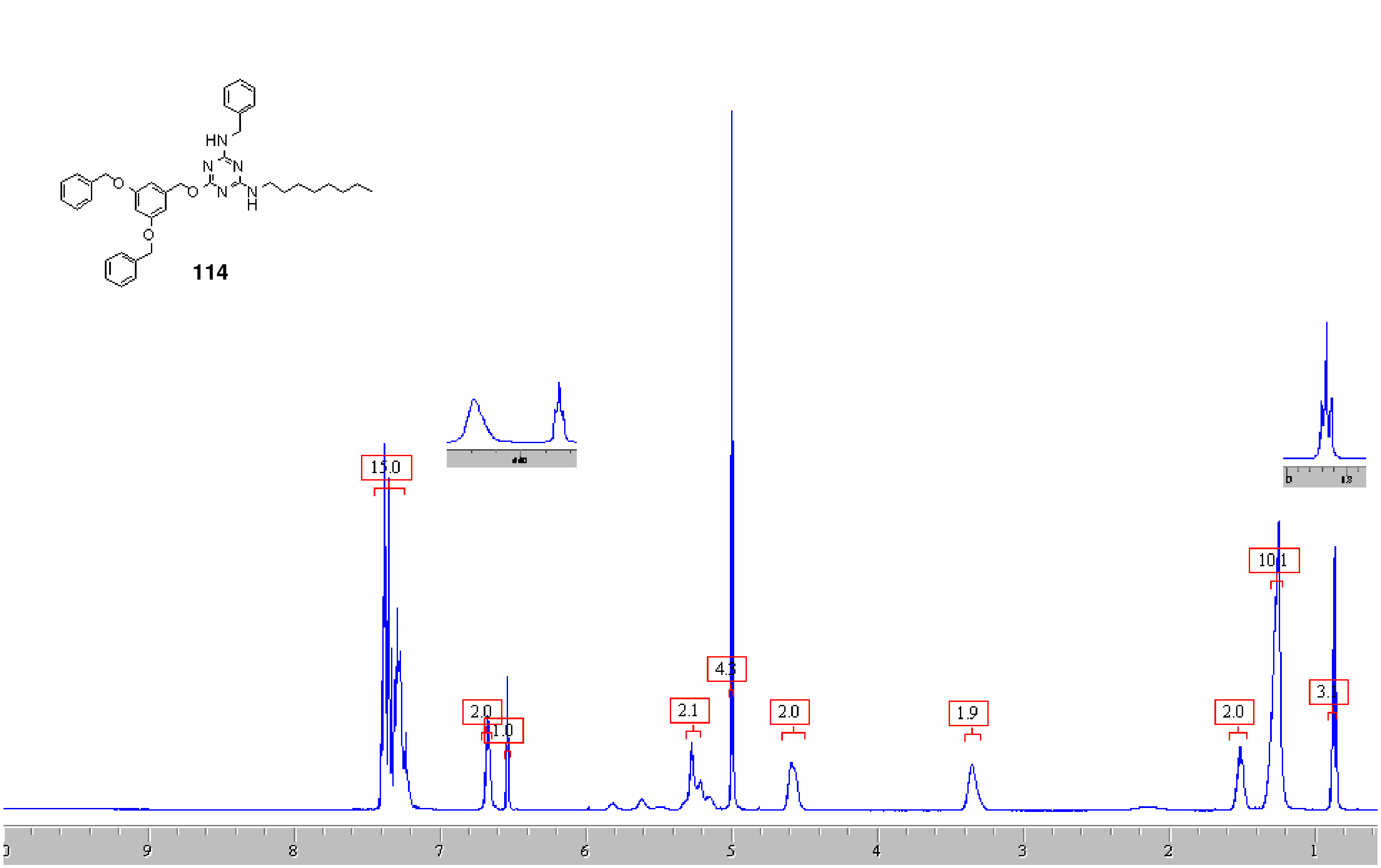


Figure A.51. ^{1}H NMR spectrum of trisubstituted triazine **114** – Route A

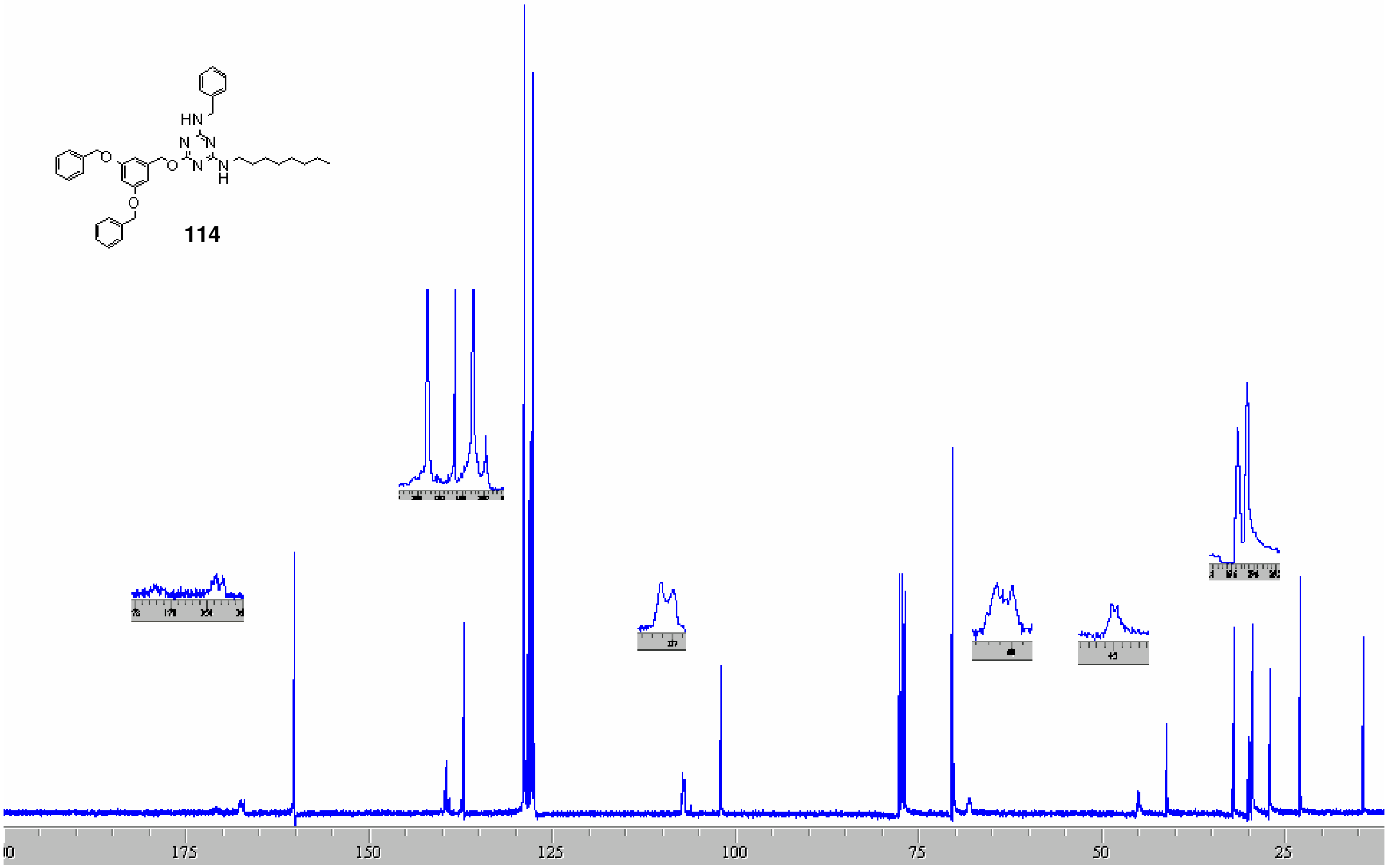


Figure A.52. ^{13}C NMR spectrum of trisubstituted triazine **114** – Route A

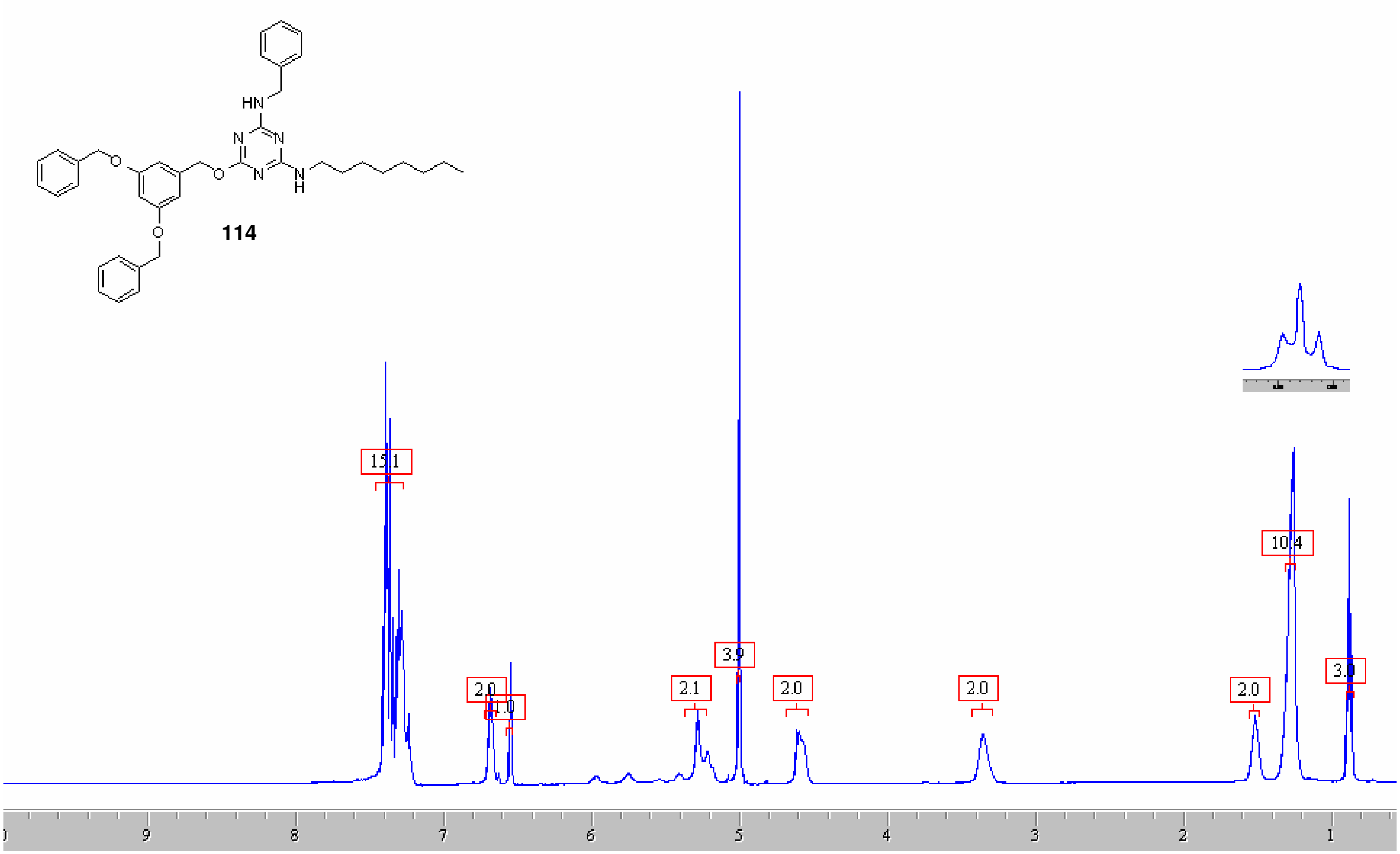


Figure A.53. ^{1}H NMR spectrum of trisubstituted triazine **114** – Route B

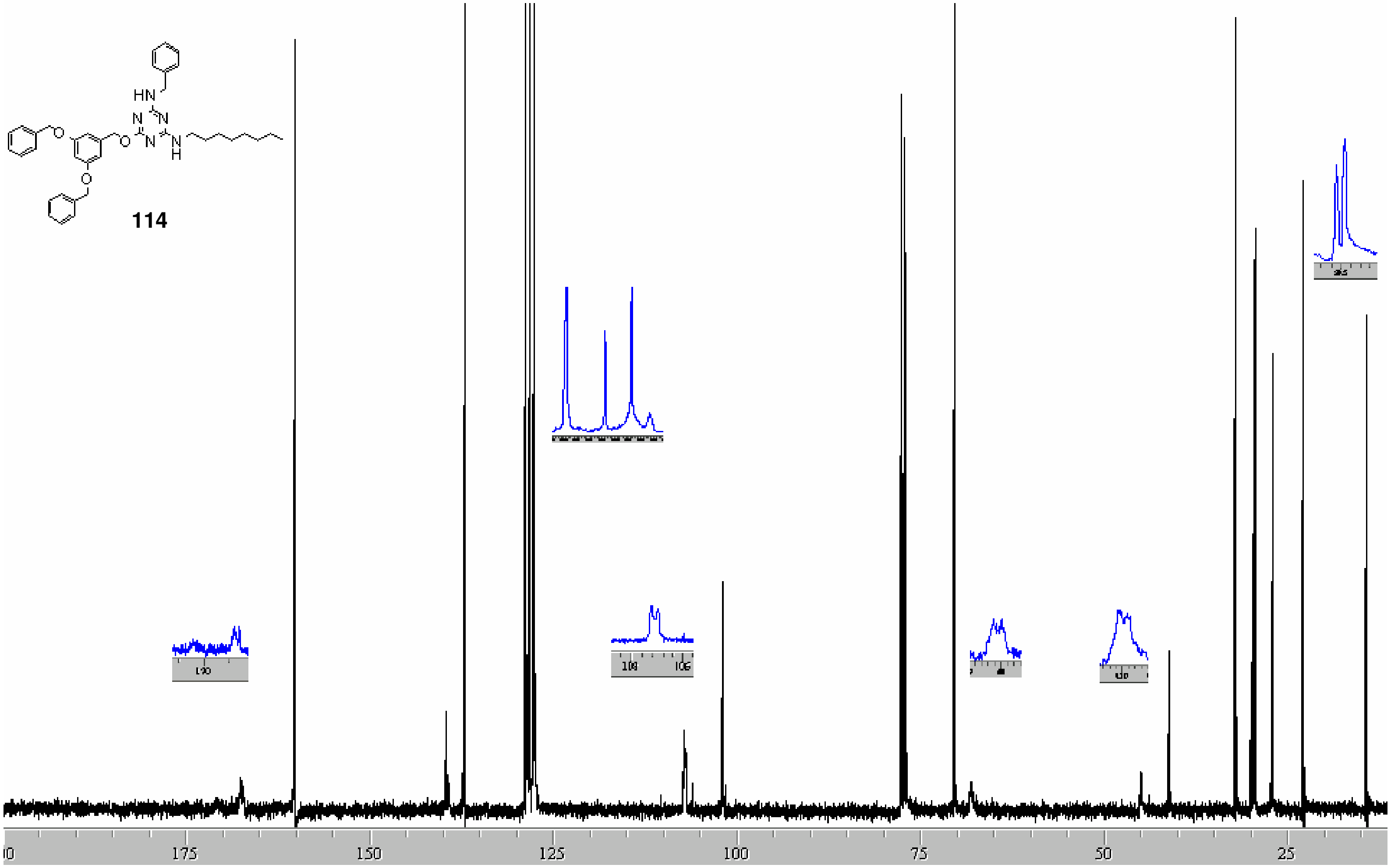


Figure A.54. ^{13}C NMR spectrum of trisubstituted triazine **114 -** Route B

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